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PART I

BLOOD VOLUME SHIFTS AND CARDIORESPIRATORY FLUCTUATIONS IN RESPONSE TO LOWER BODY NEGATIVE PRESSURE

ABSTRACT

Breath-by-breath measurements of pulmonary capillary O_2 transfer and ventilation with a box-balloon spirometer and mass spectrometer were made on 3 subjects before, during and after 10 min of lower body negative pressure (LBNP) at -20, -40 and -60 Torr with arterial samples at -60 Torr. Deficits in blood O_2 stores (O_2B) were noted during LBNP with repayment of O_2B during recovery being related to the intensity of LBNP stress. Concurrent calf volume, measured with a Hg strain gauge, decreased towards baseline well before the peak rise in pulmonary capillary O_2 transfer after the release of LBNP which signified that O_2B changes were related to blood volume shifts. The return of O_2-depleted pooled blood to the central circulation during the first min of recovery caused significant stress-related hyperpnea which peaked near 30 sec and returned to near baseline after the first min. Three-compartment lung model analyses indicated an increase in the ventilated and unperfused lung fraction (alveolar dead-space) from 0.09 (control) to 0.17 (8th min at -60 Torr) with the effective compartment decreasing from 0.83 to 0.77. It appears that the 30% increase in ventilation equivalent was primarily the result of less effective lung perfusion during LBNP.

INTRODUCTION

Marked transient fluctuations in O_2 uptake following changes in posture have been reported previously by other investigators (17, 24) as well as from this laboratory (15, 16). These transients can be accounted for by redistribution of blood volume and changes in cardiac output without invoking any alterations in metabolic rate. While the effects of changes in ventilation, cardiac output and in the distribution of ventilation and perfusion in the lungs on gas stores in the body have been studied extensively and were recently reviewed by Cherniack and Longobardo (5), the readjustments that take place in gas exchange and storage with changes in posture have not been closely scrutinized.

Furthermore, the transient hyperpnea observed in previous studies (24, 16) immediately after returning to the supine from the upright posture called for a closer examination of its time relationship with the translocation of venous blood pooled in the lower extremities to the central volume.

Lower body negative pressure (LBNP) used in the present study as a means to alter the distribution of blood volume and flow as in orthostasis has certain advantages over the tilt-table in that the imposed stress can be precisely graded and rapidly released without motion artifacts. At the same time the gravitational conditions in the upper part of the body are not altered, so that changes in the position of the diaphragm and viscera are minimized.

When the O_2 utilized by the tissues is constant, or can be assumed to be so, the pulmonary capillary O_2 transfer ($\dot{V}O_2PC$) can be used as a quantitative indication of the translocation of venous blood to or from the lungs and can be used to derive changes in venous O_2 stores (O_2B). With concurrent measurements of O_2 uptake at the mouth ($\dot{V}O_2E$) on a breath-by-breath basis, fluctuations in lung O_2 stores (O_2L) can also be ascertained, as described in an earlier publication (16).

The purpose of this study was to evaluate changes in blood and lung O_2 stores from $\dot{V}O_2PC$ and $\dot{V}O_2E$ during and after release from three different levels of LBNP in their relation to shifts in blood volume as reflected in the waxing and waning of leg volume. In addition, the redistribution of ventilation and perfusion in the lungs during and after exposure to -60 Torr LBNP was estimated from alveolar and arterial gas measurements.

METHODS

Subjects and Equipment

Three healthy males served as subjects in the study. Their ages were 31, 32 and 65 yr with a mean height and weight of 180 cm and 74.5 kg respectively. All tests were done at an ambient temperature of 24°C and an elevation of 5,400 feet in Albuquerque (P_B = 630 mmHg).

The LBNP box was constructed of plywood with a semicircular opening at one end partially covered by an adjustable sliding baffle which was padded with bubble plastic when sealing the subject at the illiac crest. The entire box was wrapped in a large sheet of clear plastic which was tightly secured at the subject's waist with a Velcro belt. An adjustable padded saddle attached to the floor of the box prevented the subject from being drawn into the box and bracing his feet against the bottom during LBNP. Ports lead through the walls of the box and plastic cover for pump attachment (vacuum cleaner), ventilation line and manometer. Negative pressures to -60 Torr could be attained in a few sec and held at any level with a variable leak (3-way stopcock) in the venting line. This leak, even at -60 Torr, was sufficient to provide enough ventilation through the box to prevent an increase in temperature. Ambient pressure could be re-established immediately by fully opening the leak valve.

Subjects breathed continuously through a Rudolph valve during the time of measurements. A 110-liter bag-box system with attached 6-liter Krogh spirometer was used to obtain inspired minute ventilation ($\dot{V}_I$), inspired tidal volume (V_T) and respiratory frequency (f) on a breath-by-breath basis. A respiratory mass spectrometer (SRI-MEDSPECT) was used to continuously record O_2, CO_2 and Argon from the Rudolph valve, thereby giving end-tidal ($P_{ET}O_2$ and $P_{ET}CO_2$) and mixed-expired values for O_2 and CO_2 during each breath by planimetry. The electrical signals of the gases and spirometer were recorded on a Visicorder (Honeywell-1508A). The end-expiratory lung volume for each breath was obtained from the lung volume measured by a subsequent Argon rebreathing maneuver which was adjusted for changes in end-tidal volume on the spirometer. The calculation of $\dot{V}O_2PC$, $\dot{V}O_2E$ and the pulmonary capillary gas exchange ratio (Rpc) have been described in detail in an earlier publication (16).

The circumference of the left calf was recorded continuously with a mercury-in-silastic strain gauge (Model 270 Plethysmograph, Parks Electronic Laboratories) on the Visicorder. The calibration and attachment of the gauges and the calculation

of leg volume (LV) closely followed the procedure described by Holling et al. (12). A deflection of approximately 50 mm for a 1.0% change in calf circumference resulted from this arrangement. While in the box the subject's left knee was supported in a slightly flexed position on a foam rubber cushion.

Heart rate (HR) and blood pressure were taken manually each min before, during and after LBNP with a sphygmanometer placed on the right arm.

The arterial blood samples were collected before, during and after the exposure to -60 Torr from the brachial artery through an indwelling needle. These blood samples were subsequently analyzed for hemoglobin concentration (Hb) by the cyanmethemoglobin method with a spectrophotometer (Beckman, Model D.U.). The arterial blood gases (PaO_2 and $PaCO_2$) and arterial pH were measured with a Corning (Model 16) electrode system. In all cases steady state gas exchange was measured by Douglas bag technique before, and 7.5 min after the onset of LBNP with O_2 and CO_2 concentrations measured by mass spectrometer calibrated from known gas mixtures analyzed by the Scholander technique.

The distribution of ventilation and perfusion in the lungs ($\dot{V}/\dot{Q}$) was quantitated by the 3-compartment lung analyses of Workman (35). This model estimates $\dot{V}/\dot{Q}$ in terms of the fractions of ventilated and unperfused (Fv,up), unventilated and perfused (Fuv, p) and ventilated and perfused (Fv, p) alveoli from arterial blood and end-tidal and mixed-expired gases.

All calculations were performed with a programmable digital calculator with statistical significance ($p < .05$) being evaluated with the t-test for paired samples.

Protocol

All subjects were exposed to LBNP for 10 min during each of the three experimental sessions at -20, -40, and -60 Torr on separate days. All runs were done at the same time each day with the order of the stress being altered for each subject.

Following the attachment of the leg gauge the subject was sealed into the box (preceded by the insertion of the arterial needle under local anesthesia for the runs at -60 Torr). This was followed by a 5 to 10 min period while the Douglas bags were flushed out with the subject's mixed expired air. A 2-min Douglas bag was collected from 3.5 to 1.5 min before the beginning of LBNP. Heart rate, systolic and diastolic blood pressures were recorded each min beginning 5 min before LBNP until 5 min after LBNP. One min before LBNP

the subject was switched into the bag-box apparatus for the determination of breath-by-breath respiration. These measurements were continued for 3 min following the onset of LBNP. The subject's functional residual capacity (FRC) was then determined with the rebreathing procedure after transferring to the rebreathing bag while breath-holding. Another Douglas bag was collected from 6.5 to 8.5 min of LBNP. The subject was then again switched to the bag-box apparatus for the last min of LBNP and breath-by-breath measurements were continued for 3 min after the sudden release of LBNP after which another FRC determination was made. From 6.5 to 8.5 min after LBNP of -60 Torr an additional Douglas bag was collected to measure steady state gas exchange during the collection of arterial blood. In addition, 10 cc of arterial blood were drawn 4 other times during the experiments at -60 Torr. The control sample was drawn over a one-min interval during the expired gas collection prior to LBNP. Another was drawn during the 8th min of LBNP (steady-state) and two shorter samples were drawn during the respiratory transients within the first min of LBNP and recovery from LBNP. An attempt was made to draw these latter two samples during the time interval when the end-tidal gases demonstrated the most marked deviation from baseline as determined from a previous study (16). A 5-sec time lag was assumed from lungs to sampling site. As it turned out the sample during early LBNP was taken on the average from 47 to 65 sec after LBNP was begun and the recovery sample was taken from 26 to 52 sec after the release of LBNP.

RESULTS

The baseline levels and ventilatory, end-tidal gases, $\dot{V}O_2PC$ and LV responses during the first 3 min follwing the onset and termination of LBNP are shown in Fig 1 to 6. The responses shown represent the means of the 3 subjects at each level of LBNP.

One of the subjects (No. 3 in Table 1) demonstrated signs of syncope during the 9th min at -60 Torr and his test was terminated after 9 min with a complete set of recovery measurements being taken. His last (9th) min LBNP and recovery values were averaged with the 10th min and recovery values of the other two subjects.

Leg Volume

The increase in LV with the onset of LBNP was clearly related to the severity of LBNP (Fig 1, 3 and 5). At the end of 1 min at -20, -40 and -60 Torr LV had increased 0.8%, 1.6% and 2.0% above baseline respectively with

corresponding values at 3 min of 0.9, 1.8 and 2.5%. In each case the rise during the first min appeared to decrease exponentially with further increments taking place in linear fashion in the following 2 min. No further increase in LV took place between 3 and 10 min at -20 Torr, however, at -40 and -60 Torr additional increments of 0.5% and 1.0% respectively occurred. These findings demonstrate that the initial rise in LV as well as the near-linear second component of the LV increase were directly related to the amount of orthostatic stress.

During recovery from LBNP (Fig 2, 4 and 6) LV returned rapidly to baseline during the first 10 sec and more gradually thereafter. The half-times for complete recovery were 1.5, 2.0 and 4.5 sec following -20, -40 and -60 Torr respectively. Again the initial part of the curves appeared to fall exponentially followed by a more linear decline. Following -20 Torr LV reached baseline in 8 sec whereas 1 min following -40 and -60 Torr the LV remained elevated above baseline by 0.2 and 0.5% respectively and had not returned to baseline after 3 min.

Heart Rate and Pulse Pressure

These responses are shown in Table 1 and have been summarized in Fig 7 where mean HR and pulse pressure (PP) have been plotted as a percentage of pre-LBNP baseline. The magnitude of the changes in HR and PP are directly related to the amount of negative pressure with the changes being quite minimal at -20 Torr. For all three curves the HR and PP tended to level off after the third min but returned quickly to baseline at the cessation of LBNP. Both of the variables overshot the baseline during recovery following the termination of the higher negative pressures, however only the HR during the second and third min of recovery from -60 Torr was significantly below baseline ($p < .02$). The drop in pulse pressure during LBNP in all cases was almost entirely the result of a fall in systolic blood pressure.

End-Tidal Gases and Gas Exchange

The onset of LBNP at each level was characterized by qualitatively similar responses in $P_{ET}CO_2$ and $P_{ET}O_2$ (Fig 1, 3 and 5). In each case $P_{ET}O_2$ rose by a few Torr within 5 sec after the onset of LBNP and then remained relatively stable at this new level for the first 3 min. The average rise above baseline for $P_{ET}O_2$ for the 3 tests in the first 3 min was related to the amount of LBNP, being 3.2, 4.1 and 8.1 Torr at -20, -40 and -60 Torr respectively. From the 4th through the 10th min $P_{ET}O_2$ during LBNP fell about 1.0 Torr for all three tests remaining elevated above the pre-LBNP control level.

Following the release of LBNP $P_{ET}O_2$ showed a transient drop in all three cases, being more pronounced and occuring earlier after higher negative pressures. The values for the transient decreases from the 10th min of LBNP and the time at which the minimum value occurred were 3.9 Torr at 80 sec following -20 Torr (Fig 2) and 10.2 Torr at 30 sec and 14.1 Torr at 20 sec following the release of -40 and -60 Torr (Fig 4 and 6). In each case after about 2 min $P_{ET}O_2$ had returned to a value between the pre-LBNP baseline and 10th min LBNP value.

The changes in $P_{ET}CO_2$ were opposite to those seen for $P_{ET}O_2$, falling within 5 sec after the onset of LBNP and remained below baseline by 1.5, 1.9 and 4.2 Torr for the first 3 min at negative pressures of 20, 40 and 60 Torr respectively. These levels remained relatively unchanged until the release of LBNP when $P_{ET}CO_2$ rose earlier and in increasing magnitude with higher preceding LBNP (Fig 2, 4 and 6), but did not show marked transients like $P_{ET}O_2$.

The breath-by-breath respiratory gas exchange ratios in the pulmonary capillaries are depicted in Fig 8. In each case following the onset of LBNP, Rpc rose to a peak at 5 sec and then remained elevated above the baseline on the average over the first min with the extent corresponding to the severity of LBNP. During the remaining 9 min at -20 and -40 Torr Rpc declined slightly with a small elevation occurring towards the end with -60 Torr. After the release of -20 Torr LBNP there was no change in the average Rpc for the first min, except at 5 sec (Fig 8); however, this was the result of one subject taking a very deep breath at this point. Following the larger negative pressures there was an initial drop between 10 and 15 sec with an overall depression over one min corresponding to the degree of negative pressure. These differences in Rpc during and after LBNP reflect large fluctuations in the relative exchange rate of O_2 and CO_2 between the lung and pulmonary capillaries.

Ventilation

The responses in ventilation to the onset of LBNP are depicted in Fig 1, 3 and 5. With -20 Torr there was a small increment in $\dot{V}_I$ during the first 15 sec of 0.30 liters, about half of which was accounted for by the FRC increase during this time of 0.14 liters (Fig 9). However, when $\dot{V}_I$ was averaged over the first min it was depressed by 5% from baseline and tended to remain slightly lower with no marked changes being evident in f and V_T (Fig 1). This same pattern was seen with 40 Torr negative pressure (Fig 3) with $\dot{V}_I$ showing a some-

what greater rise during the first 25 sec of 0.85 liters while FRC rose by 0.26 liters. Following the onset of -60 Torr (Fig 5) $\dot{V}_I$ was elevated by 1.72 liters during the first 50 sec, only a small part of this resulting from the increment in FRC (0.39 liters). In all three cases this initial rise in $\dot{V}_I$ resulted from an increase in V_T while f tended to decline. During the second and third min no consistent changes were noted in V_T and f.

Following the release of LBNP (Fig 2, 4, and 6) $\dot{V}_I$ rose during the first min by 21, 28 and 9% after -20, -40 and -60 Torr LBNP respectively. The smaller increase following -60 Torr was the result of including the subject (No. 3) in the average who was hyperventilating as a result of imminent vasovagal syncope during the last min of LBNP thereby raising the 10th min value. His $\dot{V}_I$ during the first min of recovery fell 9% while for the other subjects it rose 43% and 19% so in this case the mean of these 2 values is probably a truer reflection of the mean response (31%) than that obtained from the mean curve in Fig 6. Following -20 Torr, transient elevation of $\dot{V}_I$ resulted primarily from a rise in V_T with f increasing somewhat during the first 30 sec, however following -40 and -60 Torr V_T accounted entirely for the increment in $\dot{V}_I$ as f fell in each case. The pattern of the increase in $\dot{V}_I$ was similar in each case, always beginning immediately at release or a few sec before and then peaking between 5 and 10 sec and returning to the 10th min LBNP level in about 1 min. Following -60 Torr about 2.5 min were required for $\dot{V}_I$ to return to the pre-LBNP level which was primarily the influence of the one subject.

The mean curves for FRC for the first min following the onset and termination of LBNP are shown in Figure 9 with the average rise after onset having been noted previously. Between the first and 10th min FRC did not change appreciably during any of the three runs. During the first min of recovery FRC fell in all cases for the first 5 or 10 sec. However, after -20 and -40 Torr it had not returned completely to baseline after the first min.

O_2 Stores

The average change in lung O_2 stores (O_2L) were deduced from the mean $\dot{V}O_2$ curves shown in Fig 9. In each case O_2L was increased during the first min of LBNP. It rose by 9 cc during -20 Torr and was increased about 3 times more with LBNP of -40 and -60 Torr. In each case this rise in O_2L was about 2/3 the result of the greater FRC with 1/3 arising from the higher $P_{ET}O_2$. Following LBNP of -20 and -40 Torr there was a small reduction in O_2L of

8 cc with a more pronounced fall of 26 cc following -60 Torr. Again about 2/3 of these changes resulted from the diminishing FRC.

The loss in venous blood O_2 stores (O_2B) during LBNP were computed from $\dot{V}O_2PC$ responses in Fig 1, 3 and 5 by comparing these to the pre-LBNP baseline. Fig 1 indicates that during 3 min of orthostatic stress a reduction of 79 cc in O_2B ($p < 0.10$) resulted which is inferred from the fact that 79 cc less O_2 was taken up by the blood in the pulmonary capillaries. The cumulative loss for the same time at -40 and -60 Torr was 128 ($p < .02$) and 147 cc ($p < .005$) respectively. In each case $\dot{V}O_2PC$ did not fall below baseline until 10 to 15 sec after LBNP onset and then remained consistently below baseline. It is obvious from Fig 1, 3 and 5 that this O_2B deficit continued beyond the third min especially during -40 and -60 Torr since $\dot{V}O_2PC$ did not return to baseline. Nevertheless, the cumulative O_2B deficit for the first 3 min did become larger as LBNP stress increased.

Conversely, following the release of LBNP there was a dramatic rise in $\dot{V}O_2PC$ in each case which peaked at 5 or 10 sec and then subsided gradually to baseline with 75% of the total "repayment" of O_2B having occurred within the first min. The cumulative values of $\dot{V}O_2$ excess corresponded closely to the level of preceding LBNP with the mean value of 88 cc being consistent but not significant ($p < .10$) while the means of 231 and 313 cc after -40 and -60 Torr were significant ($p < .02$).

Correlation between LV and O_2B Fluctuations

These two variables were correlated as shown in Fig 10 from the data points from each individual. The lower right quadrant contains the 9 points corresponding to each subject's increase in LV after 3 min of LBNP and the O_2B deficit accumulated during the first 3 min. This correlation coefficient was statistically significant and indicated a direct relationship between increasing LV and O_2B loss. The upper left quadrant contains points obtained following the termination of LBNP where the drop in LV which had occurred during the first 3 min of recovery was plotted against the corresponding excess in $\dot{V}O_2PC$ or repayment of O_2B. This relationship was also statistically significant indicating that a greater reduction in LV during recovery corresponded to a larger rise in $\dot{V}O_2PC$. Since the slopes between these two regression lines were not significantly different ($p > .20$) they were combined to form the equation shown in the figure. The slope value of 82.6 indicates that a 1.0% rise in LV resulting over a period of 3 min corresponded to an 83 cc loss in O_2B and a 1.0% drop

in LV following 10 min of LBNP resulted in the repayment of 83 cc to O2B under conditions of this study.

P_{O_2} and P_{CO_2} Gradients and Ventilation

The values for arterial P_{CO_2} and P_{O_2} related to the orthostatic stress test at -60 Torr are shown in Table 2. The recovery values for the subject who experienced vasovagal symptoms (No. 3 in Table 1) prior to the termination of LBNP have been listed separately. At the beginning of LBNP both $P_{ET}O_2$ and PaO_2 increased. The rise in $P_{ET}O_2$ was about twice that of PaO_2 which resulted in a significant increase in the P_{O_2} gradient. Virtually no further changes took place during the next 7 min of LBNP. During the first min following LBNP both $P_{ET}O_2$ and PaO_2 fell significantly while in subject 3 they increased by about 5 Torr. The $a\text{-}AD_{O_2}$ showed a small decrease in all subjects in the first min of recovery. After 7 min of recovery $P_{ET}O_2$ and PaO_2 had essentially returned to the control levels for two subjects but remained elevated for subject 3. The values for P_{CO_2} showed trends opposite to P_{O_2}, whereby both $P_{ET}CO_2$ and $PaCO_2$ were reduced by 2 to 3 Torr at the onset of LBNP with a further reduction for $P_{ET}CO_2$ (3 Torr) taking place during the course of LBNP which served to enlarge the $a\text{-}AD_{CO_2}$ by a few Torr. During the first min of recovery from LBNP both $P_{ET}CO_2$ and $PaCO_2$ in the two normal subjects returned to pre-LBNP values while in subject 3 these values did not change with the removal of LBNP. Virtually no further change was noted in P_{CO_2} levels between the first and 7th min of recovery in any of the subjects.

The base excess (BE) computed from $PaCO_2$ and arterial pH, remained essentially unchanged throughout the procedure. The O2 deficit incurred during the LBNP procedure of 298 cc was estimated from Fig 5 where the value of 147 cc accumulated during the first 3 min was added to that extrapolated for the remaining 7 min between the 3rd and 10th min values for $\dot{V}O_2PC$ (151 cc). This total was practically identical to the O_2 repayment obtained from the excess $\dot{V}O_2PC$ in Fig 6.

Hemoglobin concentration (Table 2) showed no change during LBNP but increased by 1.2 g% ($p < .05$) in the first min of recovery and was still elevated 7 min later.

The changes in $\dot{V}/\dot{Q}$ estimated from the 3-compartment lung during and after LBNP are shown in Table 3 with the recovery values for subject 3 shown separately from the mean values of the other two subjects. It is apparent that the alveolar deadspace fraction (Fv, up) increased with LBNP, having nearly doubled after 7 min from the control value while the shunt component (Fuv, p) showed

a slight decline in the 7th min which resulted in a net reduction in the effective compartment (Fv, p) from 82 to 77%. The total fraction of ventilated alveoli (Fv) increased slightly while the total perfused alveolar fraction (Fp) decreased with the ventilation equivalent for O_2 showing an increase as well. With the termination of LBNP these trends were generally reversed and were most notable during the first min of recovery where Fv, up declined sharply, while Fuv, p was greatly enlarged with a small reduction in the effective compartment. The total fraction of ventilated alveoli therefore fell markedly along with the ventilation equivalent with the perfused alveolar fraction increasing. After 7 min of recovery all values had nearly returned to the pre-LBNP baseline for the two normal subjects. Subject 3 showed opposite trends from the others during recovery, whereby his fraction of ventilated alveoli increased slightly as the fraction of perfused alveoli continued to decline. These differences in $\dot{V}/\dot{Q}$ in subject 3 were apparent even after 7 min of recovery. His ventilation equivalent remained elevated during recovery whereas for the other two subjects it fell below baseline during the first min after LBNP and was close to the baseline after 7 min.

DISCUSSION

Effects of LBNP on Circulation and Blood O_2 Stores

Consistant and marked changes were noted in most variables at the onset and termination of LBNP. In general, the magnitude of these on- and off-responses were directly correlated with the intensity of negative pressure. The two obvious circulatory events related to gravitational stress are the reduction in total cardiac output ($\dot{Q}$) and the redistribution of blood volume between the upper and lower body. These two factors, along with a probable redistribution of blood flow are the primary events leading to the alteration of respiratory responses during the onset and termination of LBNP. Quantitative estimates of the extent of these circulatory changes with increasing LBNP are valuable in visualizing the magnitude of the respiratory responses.

In this study LV (%) was used as an index of blood volume shifted to and from the lower body during and after LBNP. Part of this volume change represents the translocation of plasma to the tissues by extravasation during LBNP and the reverse process during recovery. In a recent study, Foux and co-workers (9) studied the shift of the center of gravity of the body in 4 males as a measure of blood volume redistribution during LBNP. They estimated that between 1 and 2 kg

of body fluid was moved to the legs after 30 min of LBNP ranging from -30 to -60 Torr with the final fluid shift being proportional to LBNP with the rate of rise decreasing exponentially with time. At higher negative pressures they estimated that about half of the weight shift was extravascular with the remaining shift taking place within the vascular system. By interpolating their data at 10 min and correcting their results to the body weight of the subjects in this study it seems reasonable to assign values of 470, 930 and 1200 g to the conditions of our study. They also noted that following the release of LBNP, about 2/3 of the recovery had taken place within 2 min, but about 30 min were required for the center of gravity to return completely to the pre-LBNP position. In another recent study utilizing impedance plethysmography, Montgomery's group (19) determined the total leg and pelvic blood volume increases in 6 males after 5 min exposures to LBNP of -20, -40 and -60 Torr and found values of 484, 792 and 962 cc respectively. Extrapolating these values to 10 min assuming the response patterns described by Foux (9) would yield values of approximately 580, 940 and 1180 cc which are surprisingly close to the latter study. They did not attempt to separate intravascular from extravascular changes nor did they interpret the changes in blood volume after LBNP. With a study of 5 male subjects utilizing a water plethysmograph to measure LV changes, Musgrave (22) reported a LV increase of 614 cc after 5 min of LBNP at -40 Torr and stated that this was equivalent to the shift of blood taking place when man assumed the upright posture (0.5 to 0.6 liters) as reviewed by Gauer and Thron (10). After 10 min at -20 Torr they reported an increase in LV of 508 cc. Although they were not measuring pelvic blood volume, their values are in line with the other two studies at -20 Torr, but considerably lower at -40 Torr which could be accounted for by the relatively greater movement of blood into the pelvic region at higher negative pressures (19). From a study using a teeterboard Brown (4) reported a shift in the center of gravity amounting to approximately 800 and 1100 g when subjects were exposed to LBNP of -70 Torr for 1 and 4 min respectively. They also described the exponential nature of the slower rise in lower body weight with time. When LBNP was released they noted that approximately half of this weight was returned within 3 sec. In another study where 4 male subjects were exposed to LBNP of -50 Torr for about 12 min, Rowell (26) reported a reduction in central blood volume of 21% which represented about 1 liter in volume. Although other studies have reported plasma or blood volume redistribution with LBNP, the protocols have not been consistent

and leg and lower body volume changes depend critically on the part of the body measured and the time and severity of the LBNP stress (33). Although the magnitude of changes in LV (%) reported in this study agree with some others (32, 34) they can only be used as an index of total lower body changes. From the papers mentioned above which used various techniques and are in good agreement it seems reasonable to conclude that after 10 min at -20, -40 and -60 Torr the total blood volume shifted to the lower extremities is approximately 0.5, 0.9 and 1.2 liters respectively. The fraction of this volume which is extravasate and should show up as a loss in plasma fluid is difficult to assess, particularly as no changes in Hb concentration were observed until LBNP was released (Table 2). The hemoconcentration reflected in the rise in Hb cannot have occurred only after dump, but must have been going on during LBNP. This leads one to believe that the portion of blood pooled in the lower parts of the body is in effect sequestered from the general circulation and does not mix with it until after LBNP is terminated. The plasma volume loss during LBNP was calculated from the Hb values in Table 2. In a prior study (23) this laboratory reported a mean blood volume/body weight value of 75 cc/kg with no change in Hb content of red cells during LBNP in 10 subjects. This would give an average blood volume for subjects in this study of 5.588 liters. If the Hb values in Table 2 represented a true average for the whole body then the rise in Hb during the first min following LBNP indicated a loss in plasma volume of 380 cc (assuming no Hb left the circulation). After 7.5 min of recovery 48% of the plasma lost had been returned to the circulation. The LV changes in Fig 1, 3 and 5 indicate that the most rapid rise occurred within the first min after the onset of LBNP whereas extravasation is apparently a continuous function of time prevailing after the first min (9). If the increase in LV from the end of the first to the 10th min is assumed to represent fluid lost to the tissues, then by dividing the change in LV after 1 min by the LV increase after 10 min and multiplying this ratio by the total volume shifts approximated above, values of 50, 270 and 500 cc are obtained for extravascular fluid loss during the 3 LBNP tests. This leaves 450, 630 and 700 cc as the intravascular volume shift to the lower body after 10 min LBNP at -20, -40 and -60 Torr. The 500 cc value at -60 Torr for plasma loss is of similar order of magnitude to that estimated from the hemoconcentration (380 cc) noted above during the first min of recovery (Table 2). The amount of plasma lost from the circulation during LBNP is also inversely related to the rate at

which LV returns to baseline following LBNP (23). This was born out by the LV records in Fig 2, 4 and 6 wherein LV reached baseline 8 sec after -20 Torr but required more than 3 min to return to baseline after -40 and -60 Torr.

There are few studies in which $\dot{Q}$ has been measured at different levels of LBNP although the reduction in $\dot{Q}$ taking place when man assumes the upright posture has been extensively studied and found to be between 20 and 30% (10, 29). In a study on 4 male subjects with a dye-dilution technique, Rowell (26) measured a $\dot{Q}$ reduction of 28% after exposure to -50 Torr LBNP for an average of 12 min. Virtually all of this change occurred during the first 3 min. Murray and co-workers (21), also using a dye-dilution technique on 4 subjects, determined $\dot{Q}$ during 10-min successive increments of -10 Torr LBNP up to -60 Torr. They noted that $\dot{Q}$ fell in linear fashion from the control level to -50 Torr with a larger drop at -60 Torr where the subjects were near syncope. The percentage reductions at the LBNP levels at -20, -40 and -60 Torr were 8, 20 and 53%. In another study with dye-dilution techniques Stevens and Lamb (28) on 9 subjects measured $\dot{Q}$ at -25, -40, -60 and -80 Torr and found that $\dot{Q}$ fell 14, 28, 33 and 45% respectively after exposure for 3 to 5 min. The above studies indicate that it would not be unreasonable to assign values for these experiments of 10, 25 and 35% to the reduction in $\dot{Q}$ taking place after 10 min LBNP at -20, -40 and -60 Torr respectively.

Studies pertaining to the redistribution of blood flow between the body compartments exposed and not exposed to LBNP has apparently not been directly studied. Although Montgomery (19) reported a reduction in pelvic and leg blood flow with impedance plethysmography of 26, 36 and 41% after 5 min at the pressures used in this study they assumed that these values related to the reduction in hand and forearm blood flow consistently reported by other workers mainly using venous occlusion plethysmography (33). The difficulties of estimating changes in circulation rate or flow velocity from the latter technique have been pointed out by Gauer and Thron (10). Occlusion plethysmography measures a limb volume change as a function of time, which is primarily related to the sympathetic mechanisms of maintaining circulatory homeostasis by an increase in HR and vascular resistance after the initial shift in blood volume (Fig 7), rather than a change in flow velocity within the limb. If the vascular system during LBNP is assumed to consist of a dependent compartment (lower body) and one not directly affected by LBNP (upper body) and if total $\dot{Q}$ and blood pressure remain

relatively constant, then an increase in volume of the lower body will result in a reduction in flow velocity in that compartment while the volume in the upper body is reduced and flow velocity increased. Reductions in forearm volume have been reported by a number of laboratories (33, 20, 23). Thus if flow velocity is not increased proportionally to the reduction in volume of a segment of the circulation it would be interpreted as a drop in volume flow with the venous plethysmograph. The discrepancies between the volume flow and velocity flow of blood during upright and supine posture were pointed out by Bock, Dill and Edwards some 50 years ago (3) when estimating circulation time with histamine phosphate. They concluded that in the upright posture the overall velocity of blood flow was diminished and that the blood above the heart level probably circulated 2 or 3 times as fast as blood in the lower extremities. Therefore it does not seem unreasonable to suppose that blood flow through vessels of reduced size is increased in the upper body with flow diminishing in the lower body during LBNP.

These three circulatory changes, the reduction in $\dot{Q}$ and the redistribution of blood volume and flow can result in sizeable losses in O_2B (5, 16) which must be repayed during recovery. This O_2 deficit is alactacid as evidenced by no change in base excess during and after LBNP at -60 Torr (Table 2) and is closely tied to the increase in LV (Fig 10) which indicates that as more blood is shifted and pooled the greater is the O_2 deficit and subsequent repayment. In an earlier publication a simplified model was developed based on the circulatory events discussed here to account for the loss in O_2B during upright posture (16). In Table 4 we have employed the same model and assumptions (see legend) with the values for the reduction in $\dot{Q}$ and the redistribution of blood volume arrived at here, along with the assumption that blood flow is reduced by 40% in the lower body and increased by the same amount in the upper body during each LBNP exposure. The model crudely demonstrates the interrelationships of all three circulatory changes in determining the O_2 deficit. The loss in O_2B at each level of LBNP is quite similar to the repayment values ($\dot{V}O_2PC$ excess) shown in Fig 2, 4 and 6.

Effects of LBNP on Ventilation and Gas Exchange

The rise in $P_{ET}O_2$ and fall in $P_{ET}CO_2$ with the onset of LBNP are similar to those reported as a response to upright tilt (2, 24, 15) and are primarily related to an increase in the size of the alveolar deadspace fraction of $\dot{V}_I$. This

was clearly seen during -60 Torr LBNP where the unperfused and ventilated alveolar fraction nearly doubled (Table 3) and the a-A gradient for P_{CO_2} increased (Table 2). Since the changes in $P_{ET}CO_2$ and $P_{ET}O_2$ were related to LBNP severity, presumably the amount of alveolar deadspace is related to it also because of a successive lowering of pulmonary blood volume and perhaps pulmonary artery pressure (36). After the initial transients during exposure to LBNP there was also some CO_2 retention in the lower extremities concomitant with the loss in O_2B so that the nearly constant alveolar ventilation represented alveolar hyperventilation relative to the reduced $\dot{V}_{CO_2}$ which contributed to a lowering of $P_{ET}CO_2$. This hyperventilation is also indicated by the marked rise in $\dot{V}_I/\dot{V}O_2$ (Table 3) in all subjects lasting throughout the LBNP procedure at -60 Torr.

Total ventilation remained relatively constant after the onset of all 3 levels of LBNP (Fig 1, 3 and 5) except for the first 30 sec where the FRC became larger and CO_2 output was transiently increased as indicated by the rise in Rpc (Fig 8). During the initial stages of LBNP there may also have been some neurogenic stimulation of $\dot{V}_I$ since Rpc remained elevated well after the increase in FRC had taken place (Fig 9) and the rise in $\dot{V}_I$ was only partially accounted for by the increase in lung volume. The effect of the FRC rise on O_2L is noted in Fig 9 where the majority of the rise in O_2L occurred while FRC was increasing. The relationship between the magnitude of the FRC change and LBNP stress may reflect both a greater caudad shift of the diaphragm with higher LBNP or a relatively greater drainage of blood from the lung during the first 10 sec of LBNP which would increase the gas space in the lung (27). The 10 sec changes in LV relative to the assumed total changes indicate that at this time approximately 120, 280 and 340 ml of blood were shifted to the lower body as LBNP increased which are similar to the changes in FRC of 160, 240 and 440 ml.

The most striking changes in gas exchange and ventilation occurred after the sudden release of LBNP and were undoubtedly related to the influx of blood previously sequestered in the lower body and the altered blood gas composition of this blood as it entered the lungs and thoracic circulation. The fact that LV began to fall instantaneously upon release of suction (Fig 2, 4 and 6) points to an immediate return of this blood in near bolus fashion which is virtually complete within the first min of recovery. By measuring X-ray absorption of lung fields Kjellberg's group (13, 14) measured the influx of blood to the lungs following the release of occlusion cuffs on the legs and noted that it required only 2 or 3 sec

for the blood to appear in the lungs. They noted a peak in pulmonary blood volume at 15 sec with another inflection at 40 sec along with a peak in the size of the left ventricle at 12 sec. They also noted a marked reduction in HR during the time when the blood volume in the lungs was increasing. In this study a significant drop in HR below pre-LBNP values was also noted during the first 2 min following -60 Torr which has also been described by other experimenters (4). This phenomenon is most likely due to a sudden inhibition of the vasomotor centers and excitation of the vagal center by the increased hydrostatic pressure of blood returning to the heart acting on the baroreceptors.

The influx of this blood with an O_2 content below that of normal venous blood undoubtedly accounts in part for the rise in $\dot{V}O_2PC$ (Fig 2, 4 and 6) and the early reduction in O_2L (Fig 9). The additional O_2 uptake peaked at about 10 sec in each case, then fell gradually as the blood was resaturated which probably required more than one circulation time. The slightly longer time taken for the maximum transient deflections in $P_{ET}CO_2$ and $P_{ET}O_2$ to occur probably related to the time required for this phenomenon in the pulmonary capillaries to be seen at the mouth during subsequent exhalations. The transient drop in Rpc (Fig 8) at the time of the end-tidal gas transients after -40 and -60 Torr may reflect three factors. One is that CO_2 output is temporarily reduced relative to O_2 uptake with the sudden influx of venous blood because of the CO_2 storage in lung tissue (7); secondly, CO_2 retention during LBNP was relatively less than O_2B depletion and so relatively less CO_2 was unloaded; thirdly, the CO_2 storage capacity of the leg tissue may also have retarded the early elimination of CO_2 with the translocation of blood from legs to upper body. All these factors would dampen the rise in $P_{ET}CO_2$ relative to the drop in $P_{ET}O_2$ seen during recovery from LBNP. The transient engorgement of the lungs with blood during recovery from LBNP might also reduce the FRC although in this case the postulated volume of blood returned in the vasculature (450, 630 and 700 cc) was consistently larger than the reduction in FRC (Fig 9).

Although no direct measure was available of the O_2 content of blood towards the end of LBNP in the lower extremities it can be assumed that all of the $\dot{V}O_2$ excess seen during recovery must have resulted from the resaturation of this blood as cardiac output and the distribution of blood volume and flow returned to the pre-LBNP state. Reeves et al. (25) have measured the femoral $avDO_2$ in man during supine (4.1 vol%) and upright posture (12.3 vol%). If the latter

value holds for the entire estimated intravascular blood volume of 630 cc shifted to the lower body at -40 Torr for this study it would require .123 x 630 = 77 cc of O_2 to resaturate this blood when it passed through the lung after LBNP. However this is only about 1/3 of the 231 cc of O_2 repayed (Fig 4) and the rest of the O_2B deficit can only be accounted for by also considering the redistribution of blood flow and reduction in $\dot{Q}$ as discussed previously (Table 4).

The average P_{O_2} of the blood returning through the lungs must be at least 20 Torr lower than that of normal venous blood if the femoral measurements of Reeves (25) apply. This transient reduction in $P\bar{v}O_2$ serves to increase $\dot{V}O_2PC$ which subsequently lowers $P_{ET}O_2$, resulting in alveolar hypoxia whereby PaO_2 is temporarily reduced. This fall in PaO_2 can act as a strong transitory stimulus to increase $\dot{V}_I$ via a larger V_T (Fig 2, 4 and 6) with the duration and magnitude of the rise in $\dot{V}_I$ being related to the amount of the blood returned and its mean P_{O_2}. That the increase in $\dot{V}_I$ corresponded to a rapid reduction in HR speaks against any sympathetic stimulation of $\dot{V}_I$ arising from the baroreflex. After the release of LBNP at each level it appeared that $\dot{V}_I$ began to increase immediately with the additional $\dot{V}_I$ being related to the severity of the preceding LBNP. The averaging in determining mean $\dot{V}_I$ in this study did not allow for an accurate discrimination of the time lag, however, it was certainly less than 5 sec. The stimulus for $\dot{V}_I$ could be the result of pressoreceptor activation from the larger incoming volume of blood or a chemoreceptor response to the higher P_{CO_2} or reduced P_{O_2} of this blood. The time lag is too short for the rise in $\dot{V}_I$ to be explained by the conventional peripheral chemorecptors and the results do not preclude the findings and theories of Wasserman (30) and Filley (8) who have presented indirect evidence for intrapulmonary chemoreceptors. These findings are in agreement with those of Mills (18) who noted some 35 years ago that the release of venous occlusion cuffs on the thighs produced transient hyperpnea within 5 sec, before stimulation of the carotid bodies (10-12 sec), the latter time lag being determined with cyanide injections.

The $\dot{V}/\dot{Q}$ changes in the lung at -60 Torr as calculated from the 3-compartment model are summarized in Table 3. The alveolar deadspace fraction of total alveoli had nearly doubled after 7 min of LBNP with little change indicated in the shunt fraction, resulting in a measurable reduction in the fraction of alveoli effective in gas exchange. A decrease in lung perfusion in the upper zones would account for these changes. Calculations with the 3-compartment model

for the transients during the first min of LBNP and recovery may not be realistic because of the fluctuations in gas exchange at this time, however since the computations were done with time-averaged values they may have some validity. The two normal subjects had a marked reduction in the alveolar deadspace fraction when LBNP was terminated, with it becoming considerably less than prior to LBNP, while at the same time the shunt component was considerably enlarged. This is indicative of hyperperfusion relative to ventilation (as indicated by Fv and Fp fractions) which was still evident after 7 min of recovery although the effective fraction returned to pre-LBNP levels after 7 min. These results are qualitatively similar to those reported by Dowell (6) in 6 subjects after 15 and 55 min at LBNP of -40 Torr using the same model. They noted complete return to baseline in the alveolar compartments 15 min after LBNP. Genin et al. (11) reported similar results for alveolar deadspace in 5 subjects after 15 min at -80 Torr, however they estimated Fv, up by the Bohr equation and did not report recovery measurements. The underperfusion of the lung during LBNP must be related to the reduction in pulmonary capillary blood volume (36) as well as the enlarged hydrostatic pressure gradient from top to bottom of the lung and perhaps the drop in pulmonary artery pressure which leaves the top underperfused relative to the lower zones (31). This will reduce the effectiveness of total ventilation indicated by the 30% increase in $\dot{V}_I/\dot{V}_{O_2}$ (Table 3). When LBNP is terminated this condition is reversed with the influx of blood causing a drop in pressure gradients and increases in pulmonary blood volume and pulmonary artery pressure. Values in Table 3 signify that the subject who experienced vasovagal symptoms showed virtually no change during recovery in his $\dot{V}/\dot{Q}$ status from that after 7 min of LBNP. His alveoli remained underperfused resulting in an enlarged alveolar deadspace (evidenced by the larger a-A P_{CO_2} gradient in Table 1), while his effective alveolar fraction continued downward even after 7 min of recovery. As a result of this ineffective $\dot{V}_I$ his $\dot{V}_I/\dot{V}_{O_2}$ during recovery remained elevated whereas that for the other two subjects quickly returned to normal. It has been demonstrated previously that hypocapnia from hyperventilation alone may result in an alteration in lung $\dot{V}/\dot{Q}$ relationships and an increase in alveolar deadspace, perhaps by a drop in pulmonary artery pressure which may persist for one hour afterwards (1). It is noteworthy that Genin et al. (11) also observed greater increases in $\dot{V}_I$ and alveolar deadspace in subjects subsequently intolerant to LBNP stress compared

to tolerant subjects and suggested that a large reduction in alveolar P_{CO_2} early during LBNP might be used as a sign of impending syncope.

REFERENCES

1. Bishop, J.M. and J. Raine. Changes in ventilation-perfusion relationships in the lung after hyperventilation. In: The Regulation of Human Respiration, edited by D.J.C. Cunningham and B.B. Lloyd. Philadelphia, PA: Davis, 1963, p. 561-563.

2. Bjurstedt, H., C.M. Hesser, G. Liljestrand, and G. Matell. Effects of posture on alveolar-arterial CO_2 and O_2 differences and on alveolar dead space in man. Acta Physiol. Scand. 54:65-82, 1962.

3. Bock, A.V., D.B. Dill, and H.T. Edwards. On the relation of changes in blood velocity and volume flow of blood to change of posture. J. Clin. Invest. 8:533-544, 1930.

4. Brown, E., J.S. Goei, A.D.M. Greenfield, and G.C. Plassaras. Circulatory responses to simulated gravitational shifts of blood in man induced by exposure of the body below the iliac crests to sub-atmospheric pressure. J. Physiol (London). 183:607-627, 1966.

5. Cherniack, N.S. and G.S. Longobardo. Oxygen and carbon dioxide gas stores of the body. Physiol. Rev. 50:196-243, 1970.

6. Dowell, A.R., P.G. Schmid, D.O. Nutter, and K.N. Sullivan. Ventilation, lung volumes, and gas exchange during lower body negative pressure. J. Appl. Physiol. 26:352-359, 1969.

7. Dubois, A.B., W.O. Fenn, and A.G. Britt. CO_2 dissociation curve of lung tissue. J. Appl. Physiol. 5:13-16, 1952.

8. Filley, G.F. and F.G. Heineken. A blood gas disequilibrium theory. Br. J. Dis. Chest. 70:223-245, 1976.

9. Foux, A., R. Seliktar, and A. Valero. Effects of lower body negative pressure (LBNP) on the distribution of body fluids. J. Appl. Physiol. 41:719-726, 1976.

10. Gauer, O.H. and H.L. Thron. Postural changes in the circulation. In: The Handbook of Physiology. Circulation. Washington, D.C.: Am. Physiol. Soc. 1965, section 2, Vol. III, p. 2409-2439.

11. Genin, A.M., V.G. Voloshin, V.I. Sokolkov, and M.A. Tikhonov. Alveolar ventilation and pulmonary blood flow during the action of negative pressure on the lower part of the body. Environ. Space Sciences. 3:467-470, 1969.

12. Holling, H.E., H.C. Broland, and E. Russ. Investigation of arterial obstruction using a mercury in rubber strain gauge. Am. Heart J. 62:194-205, 1961.

13. Kjellberg, S.R., U. Rudhe, and T. Sjöstrand. Recording of X-ray absorption by the lungs with changes in the pulmonary blood contents. Acta Physiol. Scand. 20:166-171, 1950.

14. Kjellberg, S.R., U. Rudhe, and T. Sjöstrand. The relationship between the pulmonary blood content, the heart volume and the filling rate of the left ventricle. Acta Physiol. Scand. 24:49-60, 1951.

15. Loeppky, J.A. Cardiorespiratory responses to orthostasis and the effects of propranolol. Aviat. Space Environ. Med. 46:1164 -1169, 1975.

16. Loeppky, J.A. and U.C. Luft. Fluctuations in O_2 stores and gas exchange with passive changes in posture. J. Appl. Physiol. 39:47-53, 1975.

17. McMichael, J. Postural changes in cardiac output and respiration in man. Quart. J. Exptl. Physiol. 27:55-72, 1937.

18. Mills, J.N. Hyperpnea in man produced by sudden release of occluded blood. J. Physiol. (London). 103:244-252, 1944.

19. Montgomery, L.D., P.J. Kirk, P.A. Payne, R.L. Gerber, S.D. Newton, and B.A. Williams. Cardiovascular responses of men and women to lower body negative pressure. Aviat. Space Environ. Med. 48:138-145, 1977.

20. Murray, R.H., J. Krog, L.D. Carlson and J.A. Bowers. Cumulative effects of venesection and lower body negative pressure. Aerospace Med. 38: 243-247, 1967.

21. Murray, R.H., L.J. Thompson, J.A. Bowers and C.D. Albright. Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. Am. Heart J. 76:799-811, 1968.

22. Musgrave, F.S., F.W. Zechman, and R.C. Mains. Changes in total leg volume during lower body negative pressure. Aerospace Med. 40:602-606, 1969.

23. NASA Report. A study of factors affecting tolerance of gravitational stress simulated by lower body negative pressure. In: Specialized Physiological Studies in Support of Manned Space Flight. L.B. Johnson Space Center, Houston, TX. Contract NAS9-14472, February, 1976, p. 1-60.

24. Rahn, H., and R. Ament. The effects of posture upon the gas exchange and alveolar gas composition. Dayton, Ohio: Wright Air Development Center, WADC-TR-55-357, 1955.

25. Reeves, J.T., R.F. Grover, S.G. Blount, Jr., and G.F. Filley. Cardiac output response to standing and treadmill walking. J. Appl. Physiol. 16: 283-288, 1961.

26. Rowell, L.B., J.R. Detry, J.R. Blackman, and Craig Wyss. Importance of the splanchnic vascular bed in human blood pressure regulation. J. Appl. Physiol. 32:213-220, 1972.

27. Sjöstrand, T. The regulation of the blood distribution in man. Acta Physiol. Scand. 26:312-327, 1952.

28. Stevens, P.M., and L.E. Lamb. Effects of lower body negative pressure on the cardiovascular system. Am. J. Cardiol. 16:506-515, 1965.

29. Wade, O.L., and J.M. Bishop. Cardiac Output and Regional Blood Flow. Philadelphia, PA.: Davis, 1962, p. 39-43.

30. Wasserman, K., B.J. Whipp, R. Casaburi, D.J. Huntsman, J. Castagna, and J.R. Lugliani. Regulation of arterial P_{CO_2} during intravenous CO_2 loading. J. Appl. Physiol. 38:651-656, 1975.

31. West, J.B., and N.L. Jones. Effects of changes in topographical distribution of lung blood flow on gas exchange. J. Appl. Physiol. 20:825-835, 1965.

32. Wolthuis, R.A., G.W. Hoffler, and R.L. Johnson. Lower body negative pressure as an assay technique for orthostatic tolerance: I. The individual response to a constant level (-40 mmHg) of LBNP. Aerospace Med. 41: 29-35, 1970.

33. Wolthuis, R.A., S.A. Bergman, and A.E. Nicogossian. Physiological effects of locally applied reduced pressure in man. Physiol. Rev. 54:566-595, 1974.

34. Wolthuis, R.A., A. LeBlanc, W.A. Carpentier, and S.A. Bergman, Jr. Response of local vascular volumes to lower body negative pressure stress. Aviat. Space Environ. Med. 46:697-702, 1975.

35. Workman, J.M., R.W.B. Penman, B. Bromberger-Barnea, S. Permutt, and R.L. Riley. Alveolar dead space, alveolar shunt, and transpulmonary pressure. J. Appl. Physiol. 20:816-824, 1965.

36. Zechman, F.W., F.S. Musgrave, R.C. Mains, and J.E. Cohn. Respiratory mechanics and pulmonary diffusing capacity with lower body negative pressure. J. Appl. Physiol. 22:247-250, 1967.

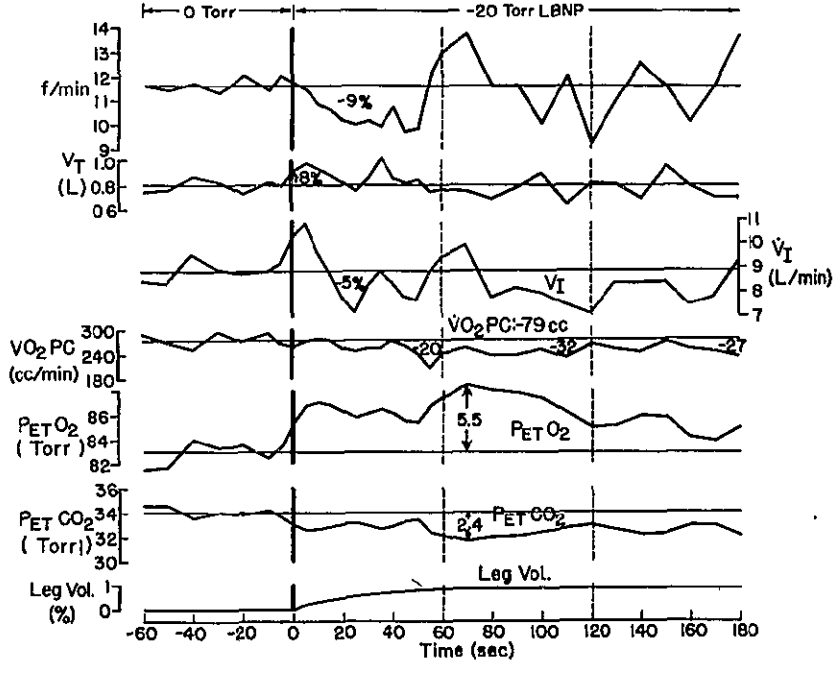


Figure 1. Tidal volume (V_T), ventilation rate (f/min), ventilation ($\dot{V}_I$), O2 intake by the pulmonary capillaries ($\dot{V}O_2PC$), end-tidal P_{O_2} and P_{CO_2}, and leg volume (L) prior to and during the first 3 min of -20 Torr LBNP. Each curve is the mean of 3 subjects.

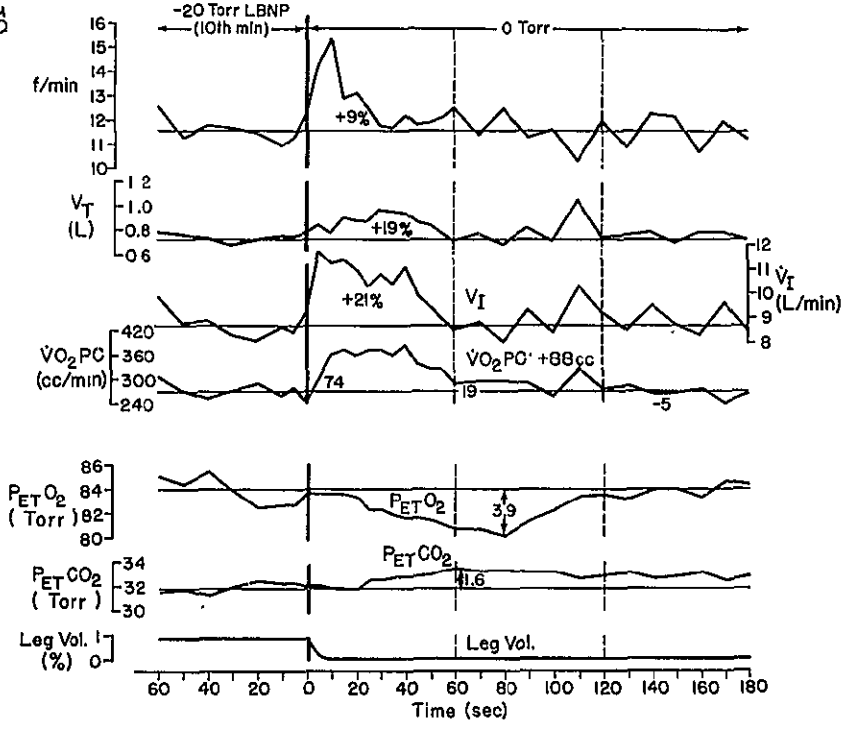


Figure 2. Same as Fig 1 for 10th min of -20 Torr LBNP and for 3 min of recovery from LBNP.

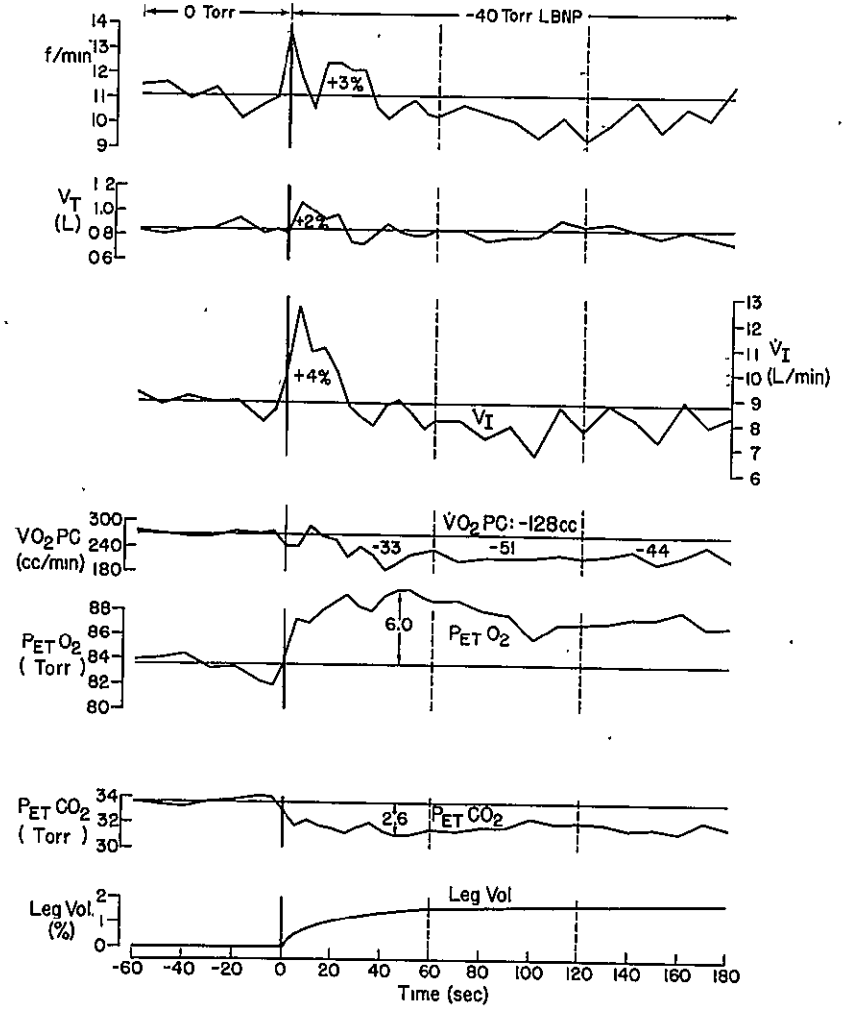


Figure 3. Same as Fig 1 for -40 Torr LBNP.

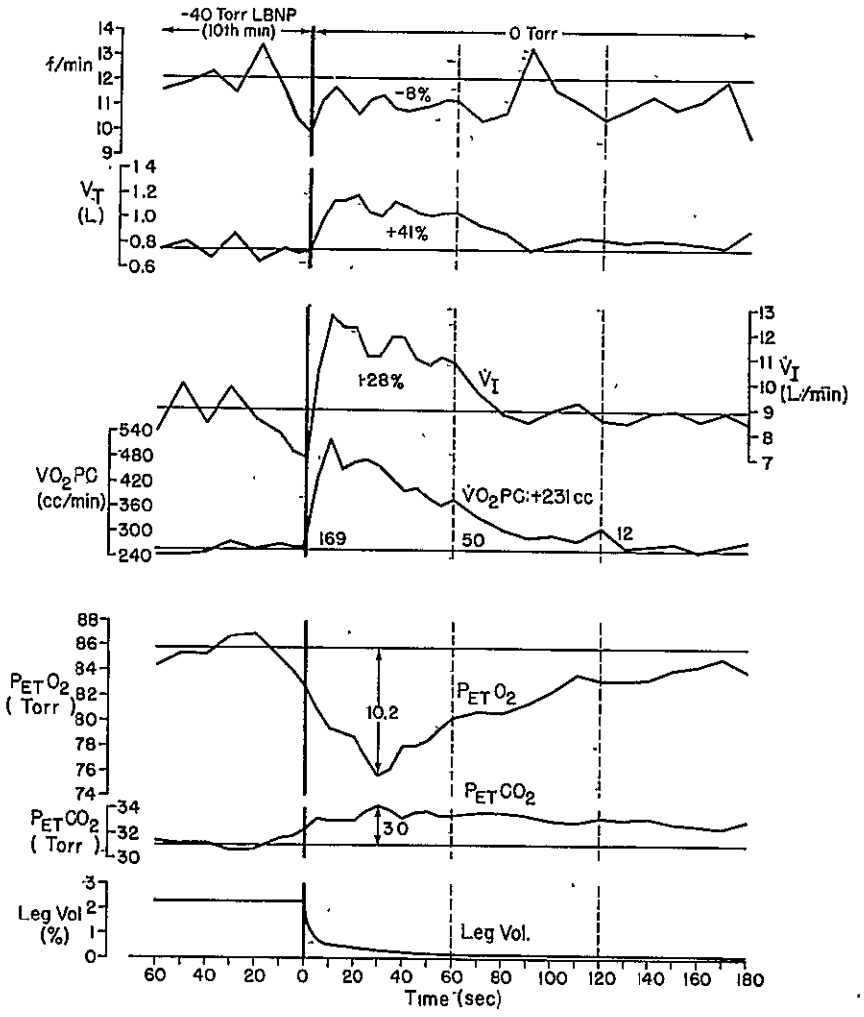


Figure 4. Same as Fig 2 for -40 Torr LBNP.

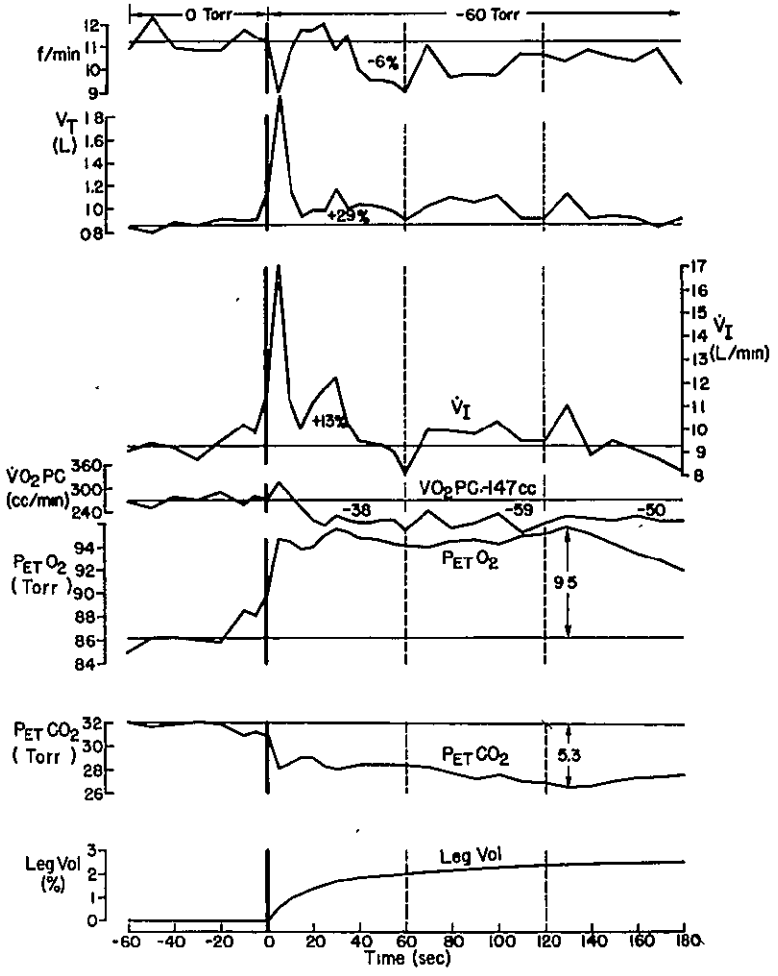


Figure 5. Same as Fig 3 for -60 Torr LBNP.

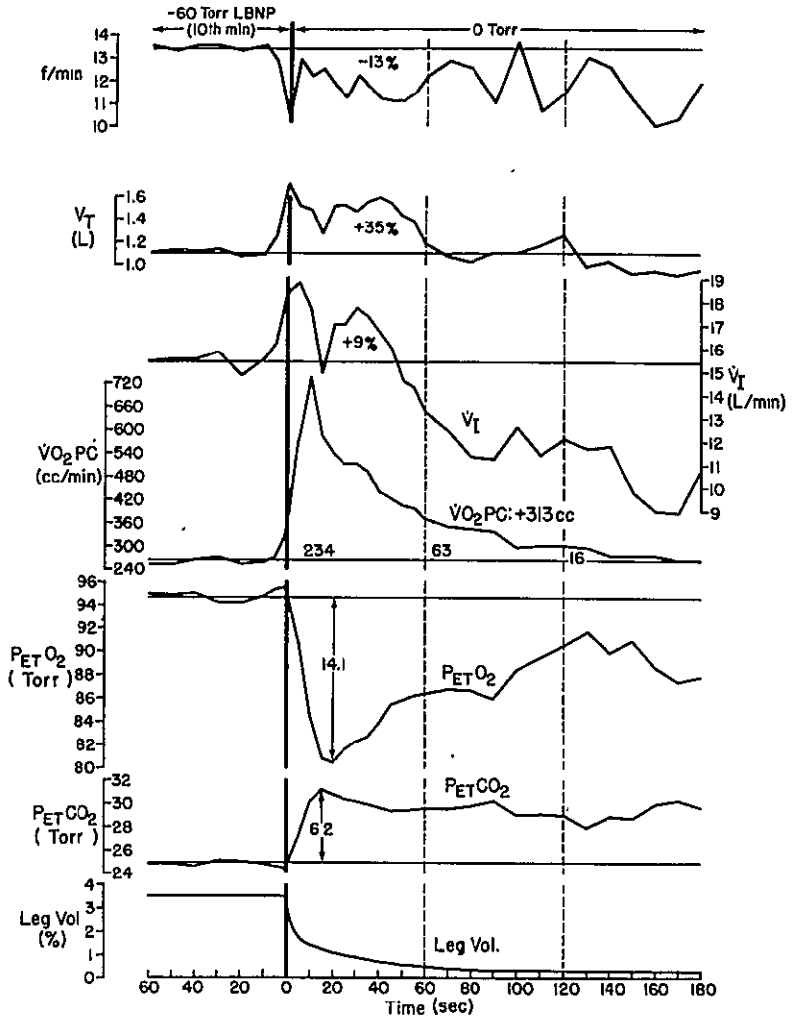


Figure 6. Same as Fig 4 for -60 Torr LBNP.

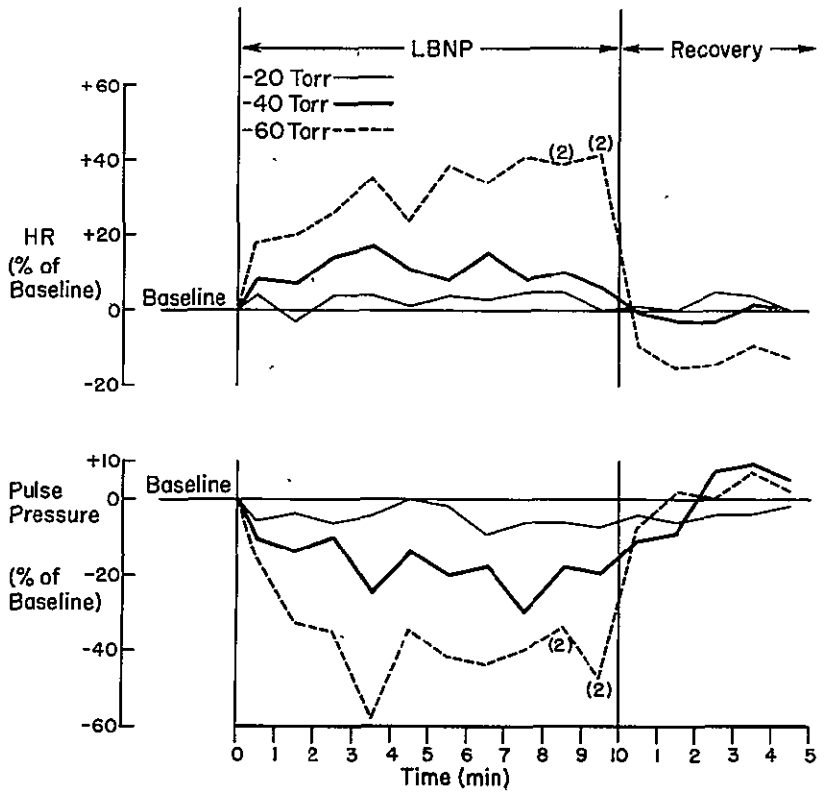


Figure 7. Mean percent heart rate (HR) and pulse pressure response of 3 subjects to LBNP of 3 intensities. Numbers in parentheses indicate n=2 since test was curtailed for one subject because of impending syncope.

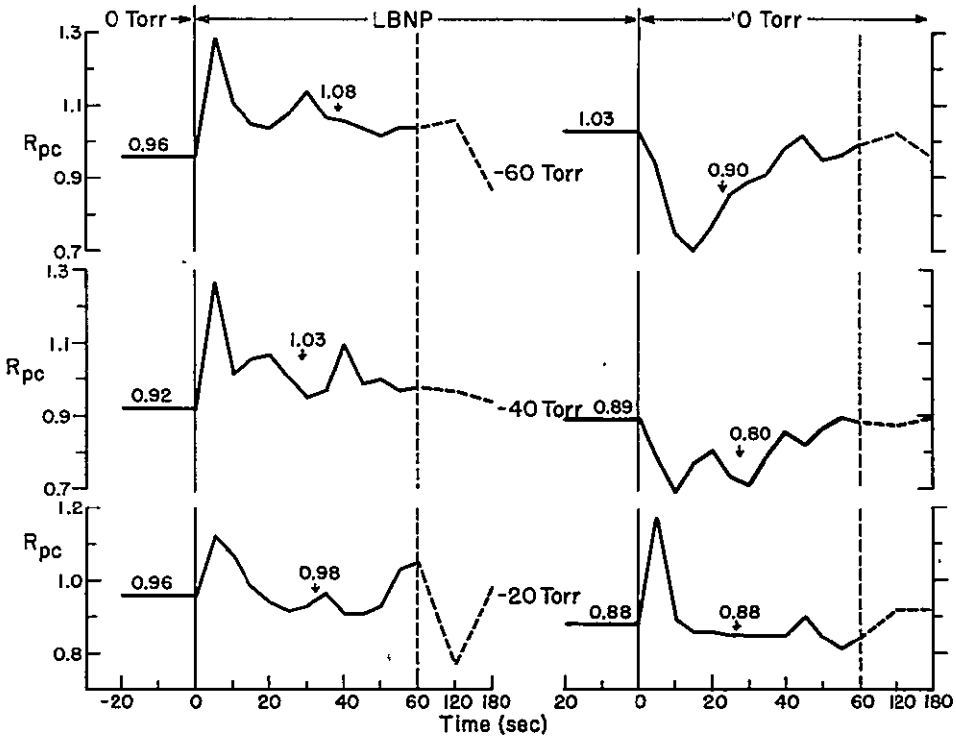


Figure 8. Mean pulmonary capillary gas exchange ratios (Rpc) of 3 subjects during the first 3 min following the onset and termination of LBNP of 3 intensities.

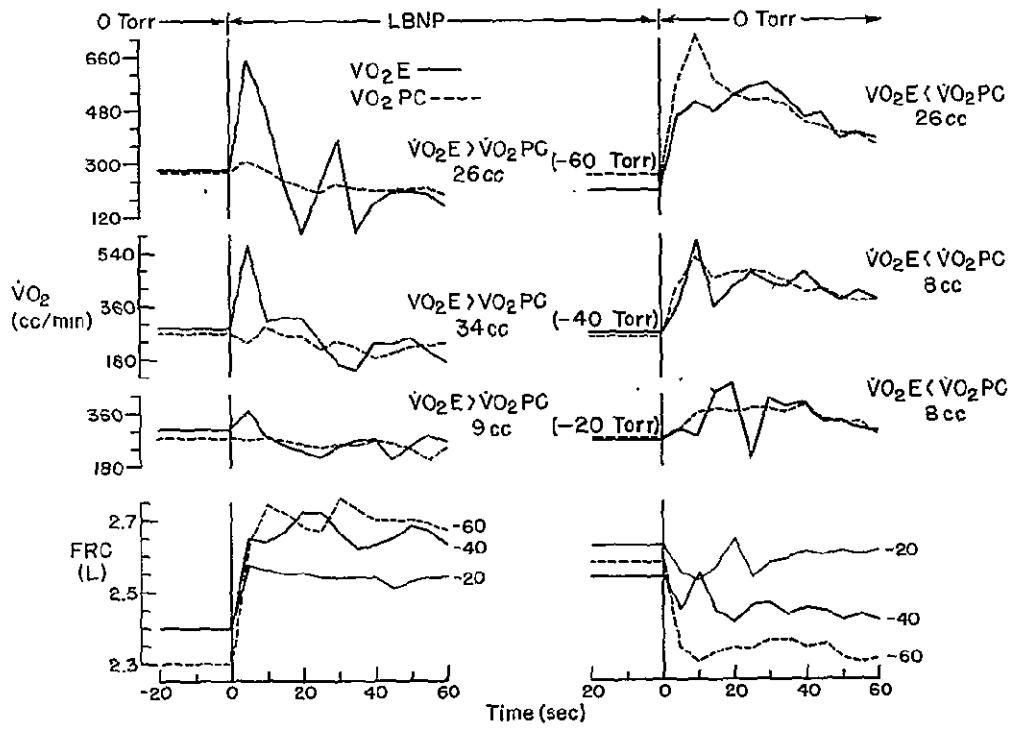


Figure 9. Average changes in lung O2 stores (O2L) and end-expiratory lung volume (FRC) in 3 subjects during the first min following the onset and termination of LBNP of 3 intensities. When O2 intake at the mouth ($\dot{V}O_2E$) exceeds that by the pulmonary capillaries ($\dot{V}O_2PC$) then O2L increases and vice-versa.

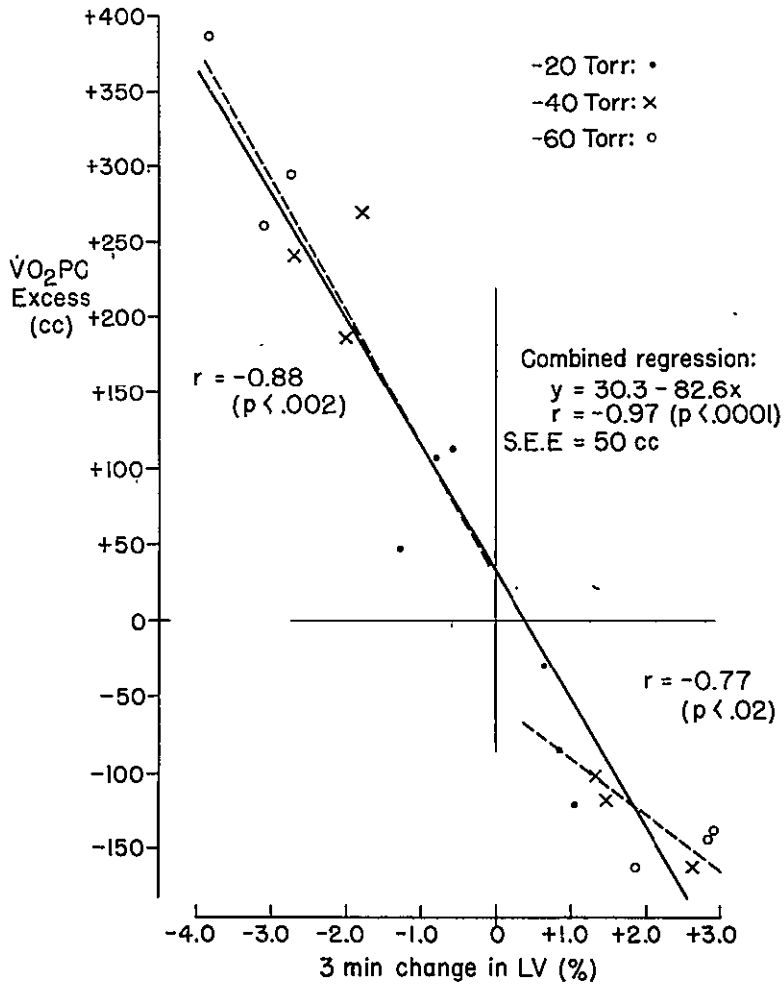


Figure 10. The relationship between the individual values for $\dot{V}O_2PC$ deficit and increase in leg volume (LV) for the first 3 min of LBNP of 3 intensities (lower right quadrant) and between $\dot{V}O_2PC$ excess and reduction in LV for the first 3 min following LBNP (upper left quadrant).

Table 1. Heart rate (HR), mean blood pressure (MP) and pulse pressure (PP) response of 3 subjects to LBNP of -20, -40 and -60 Torr.

		-20 Torr			-40 Torr			-60 Torr		
	Subj.	HR	MP	PP	HR	MP	PP	HR	MP	PP
Control (5 min)	1	85	122	60	82	118	60	86	124	60
	2	81	75	55	59	87	34	63	82	36
	3	65	85	47	70	89	39	74	87	34
	Mean	77	94	54	70	98	44	74	98	43
LBNP (1st min)	1	90	120	54	92	121	34	100	124	53
	2	82	73	50	60	83	32	82	77	28
	3	68	80	49	80	77	52	80	91	32
	Mean	80	91	51	77	94	39	87	97	38
LBNP (5th min)	1	76	121	55	100	116	36	110	121	38
	2	80	73	52	68	80	29	80	80	24
	3	77	81	56	68	80	48	88	84	25
	Mean	78	92	54	79	92	38	93	95	29
LBNP (10th min)	1	86	118	49	96	121	40	113	108	34
	2	80	74	54	60	80	30	96	82	20
	3	64	86	48	68	76	36	96•	77•	20•
	Mean	77	93	50	75	92	35	102	89	25
REC (1st min)	1	82	117	52	80	117	50	73	122	59
	2	80	75	50	62	78	35	64	83	40
	3	72	79	52	68	69	31	68	77	26
	Mean	78	90	51	70	88	39	68	94	42
REC (5th min)	1	84	121	63	84	116	54	81	120	61
	2	80	74	54	60	81	39	58	86	42
	3	68	83	44	68	86	47	68	81	32
	Mean	77	93	54	71	94	47	69	96	45

Note: Control values are averages for 5 min preceding LBNP; • : 8th min values because LBNP of -60 Torr was terminated for subject 3 after 9 min; PP and MP in Torr with MP = disatolic pressure + PP/3.

Table 2. Effects of -60 Torr LBNP for 10 min on end-tidal and arterial P_{O_2} and P_{CO_2}, blood O_2 stores (O_2B), arterial Hb concentration and base excess.

		-60 Torr LBNP		Recovery	
	Control	(47-65 sec)	7.5 min	(26-52 sec)	7.5 min
P_{ETO_2} (Torr)	84	93	91	75* (99)	85 (97)
PaO_2 (Torr)	67	71	70	57* (80)	65 (78)
$A\text{-}aDO_2$ (Torr)	17	22*	21	18 (19)	20 (19)
$PaCO_2$ (Torr)	35	33	32	35 (30)	34 (31)
P_{ETCO_2} (Torr)	33	30	27	33 (25)	32 (25)
$a\text{-}ADCO_2$ (Torr)	2	3	5	2 (5)	2 (6)
O_2 deficit (cc)	--	298		--	
O_2 repayed (cc)	--	--		313	
Hb (g%)	16.4	16.4	16.4	17.6*	17.0
B.E. (mEq/liter)	+1.6	+1.9	+1.7	+1.6	+1.5

Note: *: value differs significantly ($p < .05$) from the preceding one; parentheses: values for subject whose test was terminated at 9 min due to impending syncope; O_2 deficit calculated by extrapolating $\dot{V}O_2PC$ deficit (Fig 5) to 10 min; O_2 repayed from $\dot{V}O_2PC$ excess in Fig 6.

Table 3. Effects of -60 Torr LBNP for 10 min on $\dot{V}/\dot{Q}$ distribution estimated by 3-compartment lung model (35) and ventilation equivalent for O_2.

		LBNP -60 Torr		After	
	Control	(47-65 sec)	7.5 min	(26-52 sec)	7.5 min
Fv, up	9	11	17	4 (20)	6 (24)
Fuv, p	9	9	6	21 (4)	11 (3)
Fv, p	82	80	77	75 (76)	83 (73)
Fv	91	91	94	79 (96)	89 (97)
Fp	91	89	83	96 (80)	94 (76)
$\dot{V}_I/\dot{V}O_2$ (liter/liter)	30	43	39	26 (55)	32 (42)

Note: Fv, up: fraction of alveoli ventilated and unperfused; Fuv, p: fraction unventilated and perfused; Fv, p: fraction ventilated and perfused; Fv: total fraction ventilated; Fp: total fraction perfused; all fractions x 100; parentheses: values for subject whose test was terminated at 9 min due to impending syncope.

Table 4. Theoretical calculations with a 2-compartment circulatory system to demonstrate effects on venous O_2 stores (O_2B) of shifting venous blood volume (BV) and flow ($\dot{Q}$) and reducing total $\dot{Q}$ by LBNP.

			LBNP					
	Control		-20 Torr		-40 Torr		-60 Torr	
	U	L	U	L	U	L	U	L
$\dot{V}O_2$ (cc/min)	150	150	150	150	150	150	150	150
BV (cc)	2250	2250	1800	2700	1620	2880	1550	2950
$\dot{Q}$ (cc/min)	2500	2500	3150	1350	2625	1125	2275	975
$avDO_2$ (cc/cc)	.060	.060	.048	.111	.057	.133	.066	.154
CVO_2 (cc/cc)	.140	.140	.152	.089	.143	.067	.134	.046
O_2B (cc)	315	315	274	240	232	193	208	136
Total O_2B (cc)	630		514 (-116)		425 (-205)		344 (-286)	

Note: L: legs or dependent compartment; U: upper body or independent compartment; Compartments U and L have constant and equal $\dot{V}O_2$; CVO_2: venous O_2 content calculated as $0.20 - \dot{V}O_2/\dot{Q}$. During control BV and $\dot{Q}$ are equal in U and L (assumed total $\dot{Q}$ of 5,000cc/min and total BV of 4,500 cc). The BV shifts are 450, 630 and 700 cc during -20, -40 and -60 Torr respectively with corresponding reductions in total $\dot{Q}$ of 10, 25 and 35%. In each case $\dot{Q}$ is shifted by 40% towards U and away from L. Numbers in parentheses refer to differences in total O_2B from control.

PART II

GRAVITATIONAL EFFECTS ON BLOOD DISTRIBUTION, VENTILATION AND GAS EXCHANGE AT THE ONSET AND TERMINATION OF EXERCISE

ABSTRACT

Breath-by-breath measurements of ventilation, gas exchange, and leg volume were made on six subjects during mild exercise and recovery in the upright and supine postures. The study demonstrated that marked differences related to posture in leg volume, ventilation, and O_2 transfer at the pulmonary capillary level were evident during early exercise and recovery. Increasing venous return to the heart and lungs, inferred from leg volume measurements, and increased leg blood flow during the onset of upright and end of supine exercise could account for these differences. The replenishing of venous O_2 stores depleted prior to exercise in the upright posture accounted for the faster rise in pulmonary O_2 transfer and ventilation seen during the first 40 sec of upright exercise and a loss in lung O_2 stores during this time. These changes are quite similar to those seen after the release of LBNP. When exercise was terminated O_2 transfer fell off more rapidly while upright because venous O_2 stores were again being depleted similar to the onset of LBNP, with a drop in ventilation compared to the supine recovery. $\dot{V}O_2PC$ in early supine recovery was transiently elevated above the exercise baseline reflecting an increased venous return to the heart and lungs. In analyzing the time courses of ventilation and gas exchange at the beginning and the end of exercise the redistribution of blood volume and consequent changes in O_2 stores, which are posture dependent, should be taken into account in order to identify actual metabolic events and thus avoid errors in estimating the O_2 deficit and the early phase of the O_2 debt.

INTRODUCTION

When man assumes the upright posture with minimal assistance from the leg muscles as when sitting or supported in the upright position on a tilt-table or when he is exposed to lower body negative pressure (LBNP), a substantial volume of blood is shifted to the lower extremities. As this posture or LBNP continues over a period of minutes a relatively constant distribution of blood is attained and the volume of blood in the dependent parts of the body can simplistically be considered a "pooled" or "stagnated" compartment. Cardiovascular adjustments take place to maintain the circulatory system under these conditions of a diminished central blood volume (11,33). The increment in blood volume in the lower extremities under these conditions of a superimposed hydrostatic effect of 1.0 G is in the order of 0.5 to 1.0 liters or 20% of the total circulating blood volume (10,23,24). Under these conditions there is no evidence that the tissue O_2 requirements in the lower extremities are altered, and the O_2 content in the pooled blood will be significantly reduced and CO_2 content increased as a result of the reduction in blood flow. For example, an arterio-venous O_2 difference (AVD_{O_2}) of 14 vol% has been measured in the femoral blood in the upright posture (26). A previous study from this laboratory (19) demonstrated that when human subjects were returned to the supine position after 10 min of passively standing upright on a tilt table at 60° from the horizontal a marked increase of O_2 uptake occurred immediately at the pulmonary capillary level ($\dot{V}O_2PC$). This transient rise was 75% complete after the first min and amounted to 200 cc in total after 3 min, equalling the loss in blood O_2 stores (O_2B) incurred while upright. This repayment of O_2B was associated with a significant rise in ventilation ($\dot{V}_I$). Quantitatively similar results were obtained after the release of 10 min LBNP at -40 mmHg. The rise in $\dot{V}O_2PC$ was quite similar to the tilt table study (230 cc) with $\dot{V}_I$ showing a corresponding rise (20). In the latter study leg volume was reduced approxmately 2% within 10 sec after LBNP release, coinciding with the rise in $\dot{V}O_2PC$ and $\dot{V}_I$.

Initiating leg exercise in the upright position results in the mobilization of the pooled blood from the legs to the thorax via the muscle pump. Since this is similar in terms of blood volume shifts to the release of LBNP or the return to supine after being upright, one would anticipate a greater rise in early $\dot{V}O_2PC$ and $\dot{V}_I$ in comparing responses to those of the same subjects during

supine exercise requiring the same metabolic rate where no blood pooling had taken place prior to exercise. As early as 1913 Krogh and Lindhard (16) deduced certain circulatory changes at the beginning of exercise from corresponding alterations in O_2 uptake, but they did not consider the effects of prior venous pooling.

During recovery from upright exercise a significant volume of blood presumably again pools in the lower extremities depleting O_2B, thereby resulting in a lower $\dot{V}O_2PC$ than during recovery from supine exercise. This depletion of O_2B due to blood pooling is a much slower process than the repayment of these stores because the depletion of venous O_2B is a function of metabolic rate of poorly perfused dependent parts of the body (19).

The breath-by-breath measurement of $\dot{V}O_2PC$ is a more valid assessment of O_2 uptake during non-steady states than is $\dot{V}O_2$ measured at the mouth by open-circuit gas exchange techniques because lung stores may change during the collection period. A number of assumptions are inherent in this report: a) In a true steady state O_2 transfer at the mouth ($\dot{V}O_2E$) is equal to $\dot{V}O_2PC$ which in turn is equal to the cellular O_2 consumption or metabolic rate. Since the rate of change in cellular $\dot{V}O_2$ can not be accurately described during the onset or termination of exercise we have assumed it to be identical in both postures so that differences in $\dot{V}O_2PC$ between the two postures will be the result of variations in O_2B resulting from shifts in blood volume or flow. b) Changes in lung O_2 stores (O_2L) are reflected by differences between $\dot{V}O_2E$ and $\dot{V}O_2PC$, i.e. if $\dot{V}O_2E > \dot{V}O_2PC$ then O_2 is stored in the lung and vice-versa.

It was the purpose of this study to compare the time courses of gas exchange transients during early onset and recovery of exercise in the upright and supine posture and to determine if any differences could be ascribed to variations in concomittant blood volume and flow shifts. We also tried to determine whether the two postures would have different effects on the time course of pulmonary ventilation during the on- and off-transients of mild exercise.

METHODS

Subjects and Exercise

The supine and upright exercises were performed by 6 subjects consecutively for 8 min with at least 30 min of rest between exercises. Three subjects performed supine exercise first and the other three began in the upright position. In Table 1 are listed the physical characteristics of the subjects and their $\dot{V}O_2max$

which had been determined prior to the study by a progressive bicycle ergometer exercise in the sitting position (21). The subjects engaged in occasional endurance exercises for recreation, however none was in regular training.

The upright exercises were done on a Von Döbeln bicycle ergometer and the supine exercise on an ENSCO (Model BE-5) ergometer which was attached to the foot of a bed. Work loads on the two ergometers resulting in the same steady state $\dot{V}O_2$ (1.0 L/min) were determined with two other subjects prior to the study. This relatively low work load (35% of $\dot{V}O_2max$) was chosen to avoid exceeding the anaerobic threshold and to assure the attainment of steady state $\dot{V}O_2$ during exercise and recovery. For both exercises subjects pedalled at a rate of 40 cycles/min to a metronome. In the supine posture the feet were elevated approximately 20° above the hips while the upper body was approximately 10° above the hips. For both exercises the feet were taped to the pedals and the feet were returned to the pre-exercise position on the pedals when exercise was stopped.

Equipment and Calibration Procedures

The instrumentation and analytical procedures were quite similar to those described in an earlier study (19). Subjects breathed continuously through a Rudolph model 2600 valve (45 ml deadspace) and rubber mouthpiece. The valve was attached with corrugated plastic tubing to a 110-liter bag-in-box apparatus, forming a closed system wherein the subjects inspired humidified air from the bag and exhaled into the box. The inspiratory line was connected to a 6-liter Krogh spirometer with electrical output. Two-way stopcocks were inserted in the tubing to allow for periodic open circuit gas exchange determinations. Concentrations of O_2, CO_2, and Ar were recorded continuously with a respiratory mass spectrometer (SRI-MEDSPECT MS8) from a sampling capillary in the Rudolph valve about 3 cm from the subject's mouth. The mass spectrometer was calibrated before and after each run with gas mixtures analyzed by the Scholander technique. The electrical signals of the gases and spirometer were recorded with a Visicorder (Honeywell-1508A), providing a breath-by-breath recording on a time base. Functional residual capacity (FRC) was determined after each exercise with a gas dilution procedure, rebreathing 9% Ar in 3 liters of O_2 in a 5-liter capacity bag with attached mouthpiece and stopcock.

The areas encompassed by the O_2 and CO_2 curves during each exhalation were determined by planimetry and divided by the time from beginning to end of expiration to obtain the mixed expired gas concentrations for each breath for

O_2 and CO_2. Preliminary trials showed that these values were equal to mean mixed expired gases collected in a bag over the same period.

The volume record was corrected for time lag between spirometer and mass spectrometer and sampling rate of the latter. The spirometer was calibrated after each run with a 1.0-liter syringe. The barometric pressure and ambient temperature during the experiments were approximately 630 mmHg and 24° C respectively.

Leg volume (percent change) was obtained from continuous recordings of right calf circumference by means of a mercury-in-silastic strain gauge (Model 270 plethysmograph, Parks Electronic Laboratories) which was displayed on an oscillograph recorder (Honeywell, Model 906B). Gauge calibration and attachment as well as the subsequent calculation of limb volume change closely followed the procedure described by Holling et al. (15). During exercise the large oscillations observed in calf volume with the alternate contraction and relaxation of the leg muscles were integrated to obtain a mean value for each cycle. This was accomplished by feeding the strain gauge signal through a Krohn-Hite multi-function variable filter (Model 335, Cambridge, Mass.).

Heart rates were obtained from ECG recordings utilizing leads on the right arm, apex and forehead and were displayed on the Honeywell 906B recorder.

Protocol

After attaching ECG leads and the mercury strain gauge the subject remained at rest in the supine or upright position for 10 min before exercise began. From 4 to 1.5 min before exercise a 2.5-min Douglas bag of mixed expired gas was collected to calculate steady state gas exchange. The subject was connected to the bag-in-box 30 sec before the exercise began for baseline breath-by-breath gas exchange measurements. He began pedalling at a signal following a 5 sec count-down, reaching the prescribed rate in 2 sec or less. Breath-by-breath gas concentrations and $\dot{V}_I$ were recorded through the first 3 min of exercise. The subject was then switched from the bag-in-box and another 2.5-min Douglas bag was collected from 4.0 to 6.5 min of exercise. After 7.5 min of exercise the subject was again connected to the bag-in-box (which had been refilled with humidified air) for breath-by-breath determinations. The exercise was stopped at 8 min following a count-down and recovery gas exchange was measured for 3 min. Another Douglas bag was collected from 4.0 to 6.5 min after exercise. Three FRC determinations were then made

with the rebreathing technique, each beginning after a normal exhalation. In each case the mixed Ar concentration reached a plateau after 3 or 4 breaths with a large tidal volume. Following a rest interval the subject assumed the other posture and the entire protocol was repeated.

Calculations

The FRC for each breath was computed from the mean value obtained by the three subsequent rebreathing maneuvers, adjusted for changes in end-tidal volume on the spirometer.

Oxygen uptake was calculated at the mouth ($\dot{V}O_2E$) and the pulmonary capillary membrane for each breath according to Auchincloss et al. (1):

$$(1) \quad \dot{V}O_2PC = F_{IO_2} \cdot V_I - F_{EO_2} \cdot V_E - (F_{AO_2} \cdot V_A - \tilde{F}_{AO_2} \cdot \tilde{V}_A)$$

where F_I and F_E refer to inspired (0.2094) and mixed expired gas fractions and V_I and V_E refer to inspired and expired tidal volumes (STPD). The result of the first two terms in eq. 1 is equal to $\dot{V}O_2E$. F_A and V_A represent end-tidal gas fractions and lung volumes (FRC) at the end of the breath and $\tilde{F}_A$ and $\tilde{V}_A$ represent the same quantities at the beginning of the breath. $\dot{V}CO_2PC$ was calculated in a similar manner:

$$(2) \quad \dot{V}CO_2PC = F_{ECO_2} \cdot V_E - F_{ICO_2} \cdot V_I + (F_{ACO_2} \cdot V_A - \tilde{F}_{ACO_2} \cdot \tilde{V}_A)$$

The respiratory exchange ratio at the pulmonary capillary membrane was computed as follows:

$$(3) \quad R_{pc} = \frac{\dot{V}CO_2PC}{\dot{V}O_2PC}$$

These values were computed on a per second basis for each breath.

The respiratory frequency (f) was calculated from the time interval between successive end-expirations and was multiplied by the corresponding inspired tidal volume (V_I) to obtain $\dot{V}_I$ on a per minute basis.

Calculations were performed with a programmed digital calculator. From individual breath-by-breath values means for the 6 subjects were computed at selected time intervals before, during and after the exercise. Portions of the areas under mean curves were determined by planimetry to quantitate changes for specific time intervals. All testing for statistical significance ($p < .05$) was done with the t-test for paired samples.

RESULTS

1. Steady State Levels of Cardiorespiratory Responses

The steady state values for gas exchange were computed from the Douglas bags collected before, from 4.0 to 6.5 min during, and 4.0 to 6.5 min after exercise.

The mean FRC after recovery was 1.0 liter (BTPS) greater in the upright posture (3.92) than in the supine posture (2.92). This difference was significant ($p < .005$). The other values are summarized in Table 2. The mean $\dot{V}O_2$ during exercise was almost identical for the two exercises being 952 ± 68 cc/min during upright exercise (U) and 967 ± 71 cc/min during supine exercise (S). In percent of upright $\dot{V}O_2$max the values were 34.8 ± 5.2 and 35.2 ± 3.8 for U and S respectively. Thus, the O_2 requirements could be considered equal for the two postures. Although some differences were apparent in the various measurements between U and S in Table 2, the only ones of significance were heart rate (HR) and $P_{ET}CO_2$ before and after exercise. The HR was higher when upright in all cases, but the difference during exercise was not significant. $P_{ET}CO_2$ was 3.2 and 5.1 mmHg higher in the supine posture before and after exercise. The ventilation equivalent for O_2 was consistently but not significantly higher in the upright posture. The differences in $P_{ET}CO_2$ and $\dot{V}_I/\dot{V}O_2$ with posture signify an increase in ineffective ventilation in the upright posture compared to supine, reflecting a redistribution of ventilation and perfusion within the lung. During exercise these differences were less apparent.

2. Non-Steady State Responses to Exercise and Recovery

The average values for the breath-by-breath measurements are shown in Figs 1-4 for the first 3 min of exercise and recovery. Baseline mean values were obtained by averaging the mean curves for 30 sec preceding exercise and recovery.

Leg Volume

The mean responses are shown in Fig 1 and 2. Although leg volume (LV) is shown to have the same baseline for U and S in order to compare relative changes with each exercise, in actual fact LV is in the order of 3% greater in the upright posture (3 l) so that during exercise the absolute LV values were probably nearly equal.

first 15 sec after S there was a transient rise in $\dot{V}O_2PC$ above the exercise level amounting to 20 cc of O_2. Although not statistically significant this transient rise was noted in all but one subject. The relatively larger increase in O_2B at the start of U thus appeared to be compensated by the relatively greater loss in O_2B during recovery. The mean $\dot{V}O_2PC$ recovery half-times for U and S were 25 and 35 sec respectively.

End-Tidal Gases and Gas Exchange

The mean $P_{ET}O_2$ values showed opposite courses during the first 15 sec of exercise (Fig 1) falling 1.7 mmHg with U and rising 2.8 mmHg with S after 10 sec, the latter difference being significant ($p < .005$). The $P_{ET}O_2$ time courses for both exercises were parallel after 15 sec, being offset by approximately 3 mmHg after 45 sec, the same amount as during the pre-exercise baseline. $P_{ET}O_2$ for both exercises showed a significant, but transient drop at 45 sec, being 6 mmHg below baseline in each case ($p < .05$) followed by a 2 mmHg rise during the next 10 sec. Divergent trends were again apparent during the first 15 sec of recovery (Fig 2) with $P_{ET}O_2$ falling by 1.5 mmHg after S and rising 3.0 mmHg after U ($p < .05$). During the second min of recovery both values plateaued about 7 mmHg above the exercise level.

The trends for $P_{ET}CO_2$ (Fig 3 and 4) were reversed from those of $P_{ET}O_2$. After 10 sec of exercise $P_{ET}CO_2$ fell 1.5 mmHg with S and rose 1.2 mmHg with U ($p < .05$). Both curves peaked at about 45 sec, levelled off at 90 sec and thereafter remained parallel but offset by about 2 mmHg. After 15 sec of recovery $P_{ET}CO_2$ had risen 1.5 after S and fallen 1.8 mmHg after U with both curves levelling off at 90 sec about 3 mmHg below exercise level.

The respiratory exchange ratio at the pulmonary capillary level (Rpc) during the first 20 sec of exercise (Fig 1) was markedly affected by posture. Rpc decreased by 0.30 after 5 sec of U and increased by 0.13 with S, this difference in trends being statistically significant ($p < .02$). The relatively high baseline Rpc was the result of a transient hyperventilation prior to U. After 20 sec of exercise Rpc remained fairly similar for both exercises. No marked differences were apparent during the 3 min of recovery, however Rpc after S fell during the first 5 sec and then increased for the next minute whereas Rpc after U remained fairly level.

During the first 40 sec of exercise the average Rpc was 0.87 for U and 0.98 for S (Fig 1). These values signify that $\dot{V}CO_2PC$ during U was retarded relative to $\dot{V}O_2PC$ whereas during S the gas transfer of O_2 and CO_2 were nearly equal.

The postural difference in $\dot{V}CO_2PC$ was thus about two-thirds that of $\dot{V}O_2PC$ (136 cc) at the start of exercise. During the first 100 sec of recovery the mean Rpc after U was again lower than after S (1.06 vs 1.12), indicating that CO_2 transfer to the lungs recovered slower during S than $\dot{V}O_2PC$. This is indicated by the upward trend in Rpc from 5 to 70 sec following S (Fig 2). The lag in $\dot{V}CO_2PC$ recovery following S resulted in a $\dot{V}CO_2PC$ difference which was about 50% greater than the $\dot{V}O_2PC$ difference of 152 cc.

Ventilation

The differences seen in $\dot{V}_I$ with posture during early exercise corresponded to those of $\dot{V}O_2PC$. The rise in $\dot{V}_I$ was faster during U than S (half-times of 15 and 48 sec respectively) and remained higher for 80 sec (Fig 3). The greater $\dot{V}_I$ during U over the first 40 sec amounted to 2.10 liters and in spite of large individual variations (Table 3) was statistically significant ($p < .02$). The average $\dot{V}_I$ was 22% greater during the first 40 sec of U. The enhanced $\dot{V}_I$ was accomplished primarily by a relatively larger V_T (0.11 liter) whereas f was only 0.8/min higher for U. However, from Fig 3 it is apparent that V_T was mainly responsible for the greater $\dot{V}_I$ during the first 20 sec and f during the second 20 sec. After 40 sec V_T and f showed some fluctuations, but were generally independent of posture.

During recovery from U, $\dot{V}_I$ was generally less for the first 80 sec and higher than S during the second and third min. An exception to this occurred during the first 10 sec where $\dot{V}_I$ after S was significantly lower ($p < .05$). Again quantitating the individual differences over 100 sec, it was found that the average $\dot{V}_I$ was greater after S in 5 of 6 subjects, but the mean difference was not statistically significant (Table 3). The half-times for $\dot{V}_I$ from Fig 4 for U and S were 21 and 38 sec respectively, being quite similar to those for $\dot{V}O_2PC$. The greater $\dot{V}_I$ for S was the result of a larger V_T from 10 to 70 sec, with f falling from the exercise to resting level within the first 10 sec of recovery in both postures.

Lung O_2 Stores and FRC

The changes in O_2L were estimated for the first min of exercise and recovery for both postures by comparing mean breath-by-breath values for $\dot{V}O_2E$ and $\dot{V}O_2PC$ (Fig 5). When $\dot{V}O_2PC$ exceeds $\dot{V}O_2E$ then O_2L is reduced and vice versa. The net area between the two curves corresponds with the change in O_2L.

During the first min of U, O_2L decreased by 120 cc while at the same time FRC fell by 0.14 liters (Fig 1). With S, O_2L was depleted by 52 cc over the first min and FRC rose 0.13 liters.

After U, essentially no change in O_2L was apparent after the first min of recovery while the FRC (Fig 2) was slightly greater (0.12 liters) than during exercise. However after S a 117 cc reduction occurred in O_2L along with a reduction in FRC of 0.14 liters. This decrease in O_2L was similar to that seen after the onset of U with about one-half of the loss occurring during the first 10 sec.

Fig 5 clearly demonstrates that the largest losses in O_2L were incurred after the onset of U and recovery from S. Both of these transients had in common a marked reduction in LV and a small reduction in FRC. From Figs 1 and 2 it is evident that for the first min of exercise or recovery the changes in FRC were directly related to changes in LV. Although variations in FRC during the transients were small, they were consistent, e.g. the mean value after 10 sec of exercise was 0.23 liters less (U) and 0.10 liters more (S) than baseline, but both differences were significant ($p < .05$).

Heart Rates

The HR responses were significantly different with posture during the first 40 sec of exercise. The mean value in Table 3 indicates that HR increased by 12 beats/min more after 40 sec of S than U. A relatively greater rise in HR with S (10 beats/min) was also seen for the steady-state values shown in Table 2. Since stroke volume usually does not change much between rest and S (5) any increase in cardiac output is more dependent on HR than in U.

The postural difference in recovery HR was also significant (Table 3). The mean HR after 100 sec of recovery had dropped by 16 beats/min more after S, and this difference was maintained about the same throughout the steady-state measurement after 4 min (Table 2).

DISCUSSION

Rapid changes in LV were seen consistently in all of these experiments, whereby there was an increase early in S and a decrease in recovery, while exactly the opposite phenomenon occurred with U. It is well known that blood-flow increases rapidly in active muscles. Measurements of bloodflow in the gastrocnemius muscle in man with an isotope clearance method (28) have shown that flow increases instantaneously with the first contraction and reaches its maximum after 30 to 40 sec of rhythmic work. Furthermore, Guyton et al. (13)

have demonstrated an immediate increase of 40% in cardiac output when muscular activity was elicited by motor nerve stimulation in dogs with an increase of 86% within 40 sec. Rising muscle perfusion is associated with regional vasodilatation as well as higher perfusion pressure, so that one would expect an increase in volume of the active limbs. This was regularly the case in S in our study, but in U a shrinkage in LV was observed of about the same magnitude as it increased in S. Early experiments by Waterfield (31) with a water plethysmograph below the knee have shown that in the erect posture the relaxed LV is 2 to 3% greater than recumbent and that brisk contraction of the muscles reduces the volume by approximately the same amount as seen in our experiments. He attributed this to the squeezing action of the muscles on the veins and venules (muscle pump). Thus the increase in muscle volume due to hyperemia in exercise, which is undoubtedly present in U as in S, is completely masked by the greater shift of pooled blood out of the legs in U. The small but consistent difference in the changes in FRC associated with exercise in the different postures appear to be closely related to the changes in LV and probably reflect the shifts of blood volume to or from the thorax with corresponding decrease or increase in lung gas volume. Sjöstrand (27) first demonstrated such effects of redistribution of blood volume on lung gas content in developing his concept of the lungs as a blood depot.

The observed reverse shifts of blood volume with exercise in the two different postures provided valuable clues as to the origin of transient discrepancies in alveolar gas exchange and ventilation seen between the two conditions. Redistribution of blood volume to or from the central blood vessels and the lungs is always associated with alterations in O_2B which must have a transient effect on $\dot{V}O_2PC$. The following simplified calculation for the transition from rest to exercise might be appropriate to explain the observed differences in $\dot{V}O_2PC$ in our experiments, whereby it is necessary to assume values for the $AVDO_2$ in the femoral blood. Reeves et al. (25,26) did a comprehensive study of $AVDO_2$ in the systemic and femoral blood in the supine and upright position at rest and during exercise. We have used the following values from their data for a work load similar to ours in order to estimate changes in O_2B at the onset of exercise:

$AVDO_2$ (cc/Liter)

		Pulmonary	Femoral
S	Rest	39	42
	Exercise	95	131
U	Rest	53	139
	Exercise	101	139

It is noteworthy that the femoral $AVDO_2$ increases markedly with S while there is no change with U, where $AVDO_2$ in the legs is already large at rest due to sluggish circulation. Using these figures and assuming that an extra 0.5 liters of venous blood is moved from the legs to the trunk at the onset of U, the oxygenation of this blood in the lungs would increase $\dot{V}O_2PC$ by 0.5 x 139 = 70 cc. If the same volume of arterial blood were shifted into the legs during S, as indicated by the increase in LV, the amount of O_2 extracted by the tissues, namely 0.5 x 131 = 66 cc, would be borrowed from O_2B and would not appear as $\dot{V}O_2PC$. The assumption that the femoral AVDO2 in S increases so rapidly appears justified from sequential measurements of mixed venous PO_2 during early exercise by a rebreathing method by Edwards et al. (4). A significant drop in $P\bar{v}O_2$ (> 10 mmHg) was already present after 15 sec. The net result of the excess $\dot{V}O_2PC$ in U and the decrement in S represents a difference of 136 cc, as was found in our measurements. The preceding calculation does not directly take into account any differences in the redistribution of blood flow with posture during exercise. In a model developed in an earlier publication from this laboratory (19) it was shown how the redistribution of flow during changes in posture at rest could account for alterations in O_2B and $\dot{V}O_2PC$.

During recovery the relationship between changes in LV and the difference between $\dot{V}O_2PC$ in the two postures was reversed. In the supine position $\dot{V}O_2PC$ actually exceeded the level recorded during exercise in the first 20 sec and this coincided with a steep drop in LV which amounted to 3% over the first min, documenting an upsurge in venous return with a corresponding rise in gas exchange in the lungs. In the upright position LV increased by 0.6% in the first 10 sec and continued to increase at a slower rate over the next 3 min as blood accumulated in the legs again. $\dot{V}O_2PC$ was lower after U than S for more than a minute and the difference amounted to 152 cc (Fig 2). Thus O_2B is replenished again after S while it is depleted after U.

This course of events is also reflected in the behavior of $P_{ET}O_2$, $P_{ET}CO_2$ and Rpc during these experiments. The fall in $P_{ET}O_2$ and rise in $P_{ET}CO_2$ during the first 20 sec of U is compatible with a rapid influx of venous blood into the lungs, while $P_{ET}O_2$ rises in S and $P_{ET}CO_2$ drops coincident with the reduction in central blood volume while metabolic demands are being met in part from O_2B. The largest departure in the end-tidal gases from the baseline occurred at about 10 sec, the time when the difference in $\dot{V}O_2PC$ was also at its maximum. During recovery the course of $P_{ET}O_2$ and $P_{ET}CO_2$ also differed markedly, but in the opposite direction as after the onset of exercise. $P_{ET}O_2$ started to rise after U and $P_{ET}CO_2$ to fall immediately, while after S $P_{ET}O_2$ showed a momentary rise followed by a significant drop. $P_{ET}CO_2$ also showed a biphasic pattern, dropping for a few seconds and then rising a above the preceding level during exercise. The incisure in both $P_{ET}O_2$ and $P_{ET}CO_2$ probably signals the arrival of additional venous blood from the extremities coincident with the depletion of LV after S. This was also indicated by the substantial loss in O_2L following S (Fig 5) which was similar to the loss incurred during the first min of U. The passage of additional venous blood through the lung will reduce O_2L as O_2B is replenished.

The sharp drop in Rpc immediately after starting U suggests that $\dot{V}CO_2PC$ was not keeping up with $\dot{V}O_2PC$, which was rising rapidly at this point. This view is supported by the observation that the difference in $\dot{V}CO_2PC$ in the first 40 sec between U and S was only 65% of that for $\dot{V}O_2PC$. A similar phenomenon in the opposite sense was noted after S, where an elevated Rpc indicated that $\dot{V}CO_2PC$ did not subside as rapidly as $\dot{V}O_2PC$ during recovery. In other words, the on- and off-transients for $\dot{V}CO_2PC$ were slower than for $\dot{V}O_2PC$. Similar observations have been made by others, notably Linnarsson (18) who ascribed this to the much greater storage capacity for CO_2 than for O_2 in the tissues (6, 7) particularly in the lungs (3), which tends to buffer rapid transients in CO_2.

The redistribution of blood volume shown in these experiments can be reproduced artificially without exercise by applying LBNP. Metabolic processes are presumably not affected by this manipulation, so that any fluctuations in pulmonary gas exchange and ventilation are attributable to shifts in blood volume alone. In previous studies in this laboratory (to be published) it was noted that the application of -40 mmHg LBNP in the supine position, which caused

an increase in LV of about 2% as seen at the onset of S and after U, was associated with a significant reduction in $\dot{V}O_2PC$, a marked rise in $P_{ET}O_2$ and a lesser fall in $P_{ET}CO_2$. However these changes were not as abrupt as in the exercise study and were sustained for more than two min. During this time the O_2 requirements of the legs were being in part defrayed from O_2 stores in the pooled blood, thus reducing $\dot{V}O_2PC$. On releasing LBNP after a 10 min exposure, LV dropped by 1.5% during the first 10 sec and returned to the original volume after one min. The rate of $\dot{V}O_2PC$ was double the control value at 10 sec, but returned to baseline during the following two min. The peak in $\dot{V}O_2PC$ was followed shortly by a drop in $P_{ET}O_2$ of 10 mmHg and a rise in $P_{ET}CO_2$ of 3 mmHg. These fluctuations in gas exchange were much more drastic than the ones at the onset of LBNP. They signify the sudden arrival of markedly reduced blood in the lungs and are analogous to the course of events at the onset of U and the end of S in the exercise experiments. The LBNP studies demonstrate clearly what can only be inferred from the exercise tests, namely that the return of pooled blood to the lungs produces a rapid, transient increase in apparent gas exchange, whereas the redistribution of blood volume into the peripheral vascular bed is associated with a more gradual reduction in $\dot{V}O_2PC$ as some O_2B is being utilized in the periphery.

Although relatively small the described changes in O_2B at the beginning and the end of exercise will enter into the estimation of the O_2 deficit and the fast component of the O_2 debt. For instance Ceretelli et al. (2), who recently studied the on- and off-transients of exercise $\dot{V}O_2$ in the sitting and supine position, noticed that $\dot{V}O_2$ rose more rapidly during upright work (half-time 36 sec) than supine (half-time 49 sec) and that the O_2 deficit was correspondingly smaller in the former (0.73 liters) than in the latter (1.30 liters). Differences in the utilization of O_2B with posture probably contributed to these discrepancies.

The ventilatory response at the beginning of exercise followed a similar pattern in both postures. However in U the rate of increase of $\dot{V}_I$ (Fig 3) was faster with a half-time only one-third of that in S. Apparently the sudden influx of venous blood to the lungs which must have been greater in U than in S augmented the initial respiratory drive. More than 30 years ago Mills (22) demonstrated that hyperpnea can be produced in man by the sudden release of blood previously sequestered by cuffs applied to the limbs. The mean time lag was only 2 sec, a much faster response than could be attributed to systemic arterial chemoreceptors. He demonstrated by peripheral injections of

cyanide that the mean response time of the latter was about 12 sec and concluded that hyperpnea is induced via pressoreceptors in the pulmonary vasculature when more blood arrives in the lungs. Wasserman and associates (29) reported rapid hyperpnea following a sudden increase in cardiac output induced with isoproteronol or cardiac pacing in dogs which was demonstrable even after removal of the carotid sinus bodies and resection of the carotid sinus nerve. They also provided evidence suggesting intrapulmonary receptors that are responsive to the CO_2 level in the blood reaching the lungs by intravenous loading in dogs (30). This produced a rapid increase in ventilation sufficient to maintain $PaCO_2$ close to control levels despite a fourfold increase in CO_2 output. The response was not affected by resection of the carotid bodies nor of the vagus nerve (32). Other investigators have disputed the presence of pulmonary chemoreflexes sensitive to CO_2, notably Gonzales and Fordyce (12). They injected $NaHCO_3$, HCl and KCN in cold saline solutions and measured the transit time of the thermal transient to the aorta and carotid bifurcation. No responses were observed before the bolus had reached the ascending aorta and usually the carotid bifurcation. Other experiments by Levine (17) on animals after spinal cord transcetion (L-2) and carotid denervation even suggest the presence of humoral agents other than arterial CO_2, pH or O_2 saturation that stimulate $\dot{V}_I$. Furthermore, Hildebrandt and Winn (14) observed the response time of $\dot{V}_E$ and $P_{ET}CO_2$ during exercise when occlusion cuffs on the legs were suddenly released. CO_2 started to rise at 10 sec and $\dot{V}_E$ increased 15 to 20 sec after release of the cuffs which is compatible with known chemoreceptor function as sole mediators of the response. Another interesting hypothesis has been advocated by Filley and Heineken (9). They believe that alterations in the alveolar-mixed venous gradients ($A-\bar{v}$) for O_2 and CO_2 cause a chemical disequilibrium in the pulmonary microvasculature that could account for the early hyperpnea of exercise via intrapulmonary chemoreceptors. Indirect evidence for such a mechanism was obtained by manipulating the $A-\bar{v}$ gradient with appropriate inspired gas mixtures and recording the immediate ventilatory response (8).

Whether or not it was the augmented venous return and cardiac output at the start of U in our experiments that caused the faster rise in $\dot{V}_I$ or whether it was due to the high PCO_2 and low PO_2 in the pooled venous blood returning to the lungs cannot be decided from our data. However, it is clear that the initial response in both postures was faster than could be explained by known chemoreceptors and could be due either to intrapulmonary sensors or peripheral

proprioceptive reflexes. But the marked difference between U and S which appeared before the systemic chemoreceptors could have been activated speaks more in favor of pulmonary receptors being involved.

REFERENCES

1. Auchincloss, J.H., Jr., R. Gilbert, and G.H. Baule. Effect of ventilation on oxygen transfer during early exercise. J. Appl. Physiol. 21:810-818, 1966.

2. Ceretelli, P., D. Shindell, D.P. Pendergast, P.E. diPrampero and D.W. Rennie. Oxygen uptake transients at the onset and offset of arm and leg work. Respir. Physiol. 30:81-97, 1977.

3. Dubois, A.B., W.O. Fenn, and A.G. Britt. CO_2 Dissociation curve of lung tissue. J. Appl. Physiol. 5:13-16, 1952.

4. Edwards, R.H.T., D.M. Denison, G. Jones, C.T.M. Davies, and E.J.M. Campbell. Changes in mixed venous gas tensions at start of exercise in man. J. Appl. Physiol. 32:165-169, 1972.

5. Ekelund, L.G., and A. Holmgren. Central hemodynamics during exercise. In: Physiology of Muscular Exercise. Amer. Heart Assoc. Monograph No. 15, 33-43, 1967.

6. Farhi, L.E., M.S. Nesarajah, A.J. Olszowka, L.A. Metildi, and A.K. Ellis. Cardiac output determination by simple one-step rebreathing technique. Resp. Physiol. 28:141-159, 1976.

7. Farrell, E.J., and J.H. Seigel. Estimation of blood gas contents from expired air under normal and pathological conditions. Resp. Physiol. 26:303-325, 1976.

8. Filley, G.F. The hyperpnea of exercise in man. Fed. Proc. 35:633, 1976.

9. Filley, G.F., and F.G. Heineken. A blood gas disequilibrium theory. Br. J. Dis. Chest. 70:223-245, 1976.

10. Foux, A., R. Seliktar, and A. Valero. Effects of lower body negative pressure (LBNP) on the distribution of body fluids. J. Appl. Physiol. 41:719-726, 1976.

11. Gauer, O.H., and H.L. Thron. Postural changes in the circulation. In: Handbook of Physiology. Circulation. Washington, D.C.: Am. Physiol. Soc., 1965, sect. 2, vol. III, chapt. 67, p. 2409-2439.

12. Gonzales, F., and W.E. Fordyce. Evidence against a CO_2 mediated pulmonary chemoreflex in dogs. Fed. Proc. 35:553, 1976.

13. Guyton, A.C., B.H. Douglas, J.B. Langston, and T.Q. Richardson. Instantaneous increase in mean circulatory pressure and cardiac output at onset of muscular activity. Circulation Res. 11:431-441, 1962.

14. Hildebrandt, J.R., and R.K. Winn. Human cardiorespiratory responses to impulses of work during circulatory occlusion. Physiologist. 19:225, 1976.

15. Holling, H.E., H.C. Boland, and E. Russ. Investigation of arterial obstruction using a mercury-in-rubber strain gauge. Am. Heart J. 62:194-205, 1961.

16. Krogh, A., and J. Lindhard. The regulation of respiration and circulation during the initial stages of muscular work. J. Physiol. (London). 47: 112-136, 1913.

17. Levine, S. Ventilatory response to exercise of denervated extremities: observations in peripheral chemodenervated dogs. Physiologist. 19: 268, 1976.

18. Linnarsson, D. Dynamics of pulmonary gas exchange and heart rate changes at start and end of exercise. Acta Physiol. Scand. Suppl. 415: 1-68, 1974.

19. Loeppky, J.A., and U.C. Luft. Fluctuations in O_2 stores and gas exchange with passive changes in posture. J. Appl. Physiol. 39:47-53, 1975.

20. Loeppky, J.A., and U.C. Luft. O_2 stores and ventilation in response to lower body negative pressure. Physiologist. 19:275, 1976.

21. Luft, U.C., D. Cardus, T.P.K. Lim, E.C. Anderson, and J.L. Howarth. Physical performance in relation to body size and composition. Annals N.Y. Acad. Sci. 110:795-808, 1963.

22. Mills, J.N. Hyperpnea in man produced by sudden release of occluded blood. J. Physiol. (London). 103:244-252, 1944.

23. Montgomery, L.D., P.J. Kirk, P.A. Payne, R.L. Gerber, S.D. Newton, and B.A. Williams. Cardiovascular responses of men and women to lower body negative pressure. Aviat. Space Environ. Med. 48:138-145, 1977.

24. Musgrave, F.S., F.W. Zechman, and R.C. Mains. Changes in total leg volume during lower body negative pressure. Aerospace Med. 40:602-606, 1969.

25. Reeves, J.T., R.F. Grover, G.F. Filley, and S.G. Blount, Jr. Circulatory changes in man during mild supine exercise. J. Appl. Physiol. 16:279-282, 1961.

26. Reeves, J.T., R.F. Grover, S.G. Blount, Jr., and G.F. Filley. Cardiac output response to treadmill walking. J. Appl. Physiol. 16:283-288, 1961.

27. Sjöstrand, T. The regulation of the blood distribution in man. Acta Physiol. Scand. 26:312-327, 1952.

28. Tønnesen, K.H. Blood-flow through muscle during rhythmic contraction measured by ^{133} Xenon. Scand. J. Clin. Lab. Invest. 16:646-654, 1964.

29. Wasserman, K., B.J. Whipp, and J. Castagna. Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase. J. Appl. Physiol. 36: 457-464, 1974.

30. Wasserman, K., B.J. Whipp, R. Casaburi, D.J. Huntsman, J. Castagna, and R. Lugliani. Regulation of arterial PCO_2 during intravenous CO_2 loading. J. Appl. Physiol. 38:651-656, 1975.

31. Waterfield, R.L. The effect of posture on the volume of the leg. J. Physiol. (London). 72:121-131, 1931.

32. Whipp, B.J., D.J. Huntsman, and K. Wasserman. Evidence for a CO_2-mediated pulmonary chemoreflex in dog. Physiologist. 18:447, 1975.

33. Wolthuis, R.A., S.A. Bergman, and A.E. Nicogossian. Physiological effects of locally applied reduced pressure in man. Physiol. Rev. 54: 566-595, 1974.

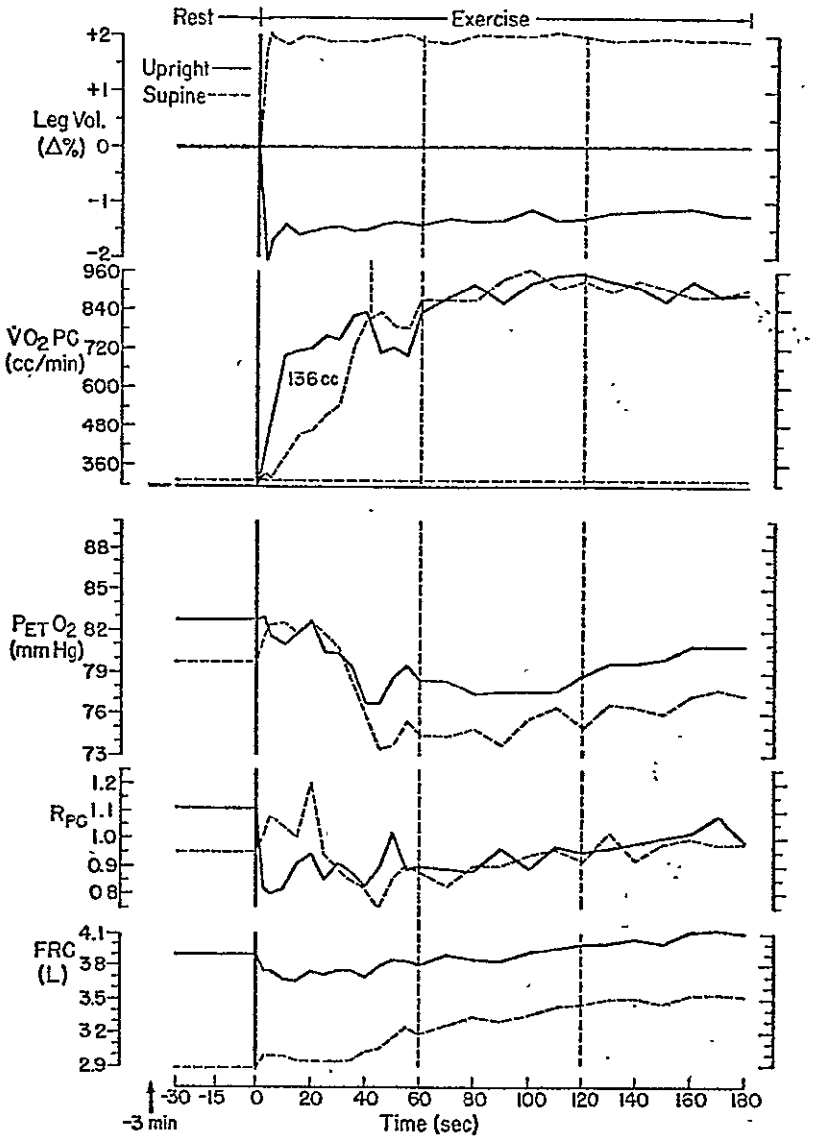


Fig 1. Right calf volume (LEG VOL.), O_2 transfer across the pulmonary capillaries ($\dot{V}O_2PC$), end-tidal O_2 pressure ($P_{ET}O_2$), respiratory exchange ratio at the pulmonary capillaries (Rpc) and functional residual capacity (FRC) at rest and during the first 3 min of exercise. Oxygen consumption was measured by Douglas bag from 4 to 1.5 min before exercise. Average barometric pressure was 630 mmHg.

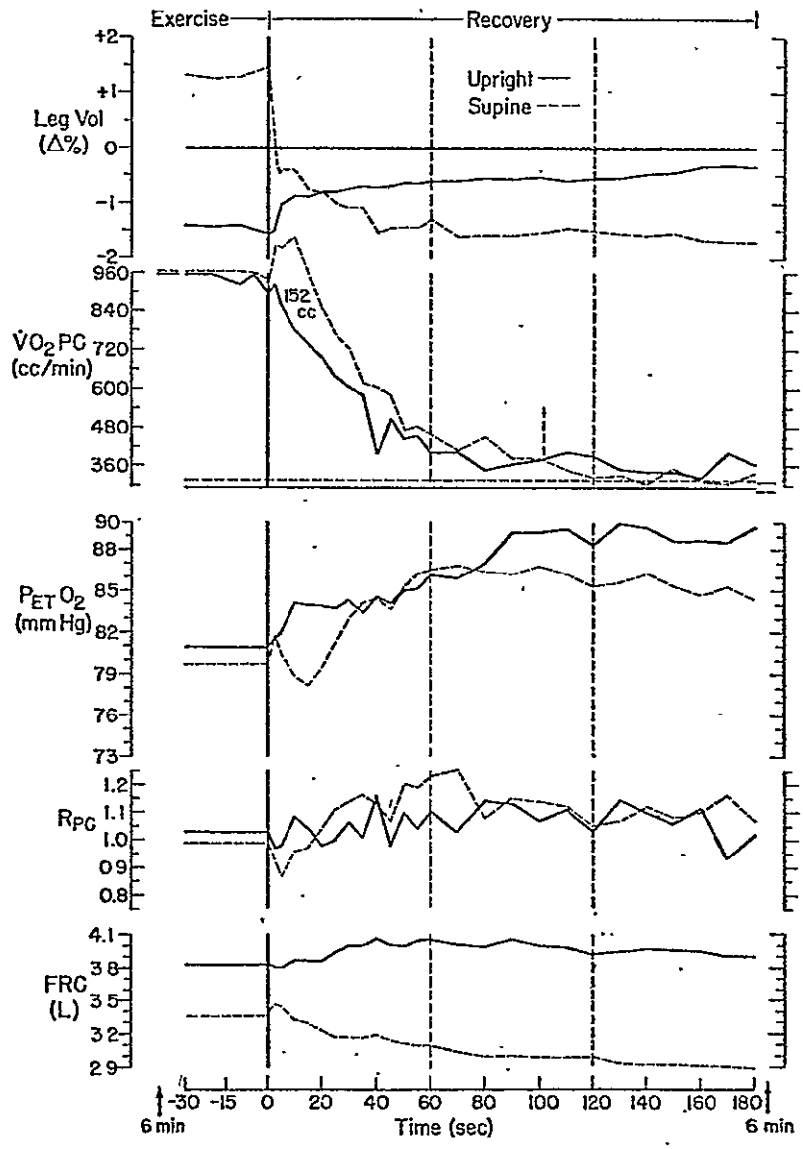


Fig 2. Same as Fig 1 for last 30 sec of the 8 min exercise and during the first 3 min of recovery. Oxygen consumption was measured by Douglas bag from 4 to 6.5 min during exercise and 4 to 6.5 min after the end of exercise.

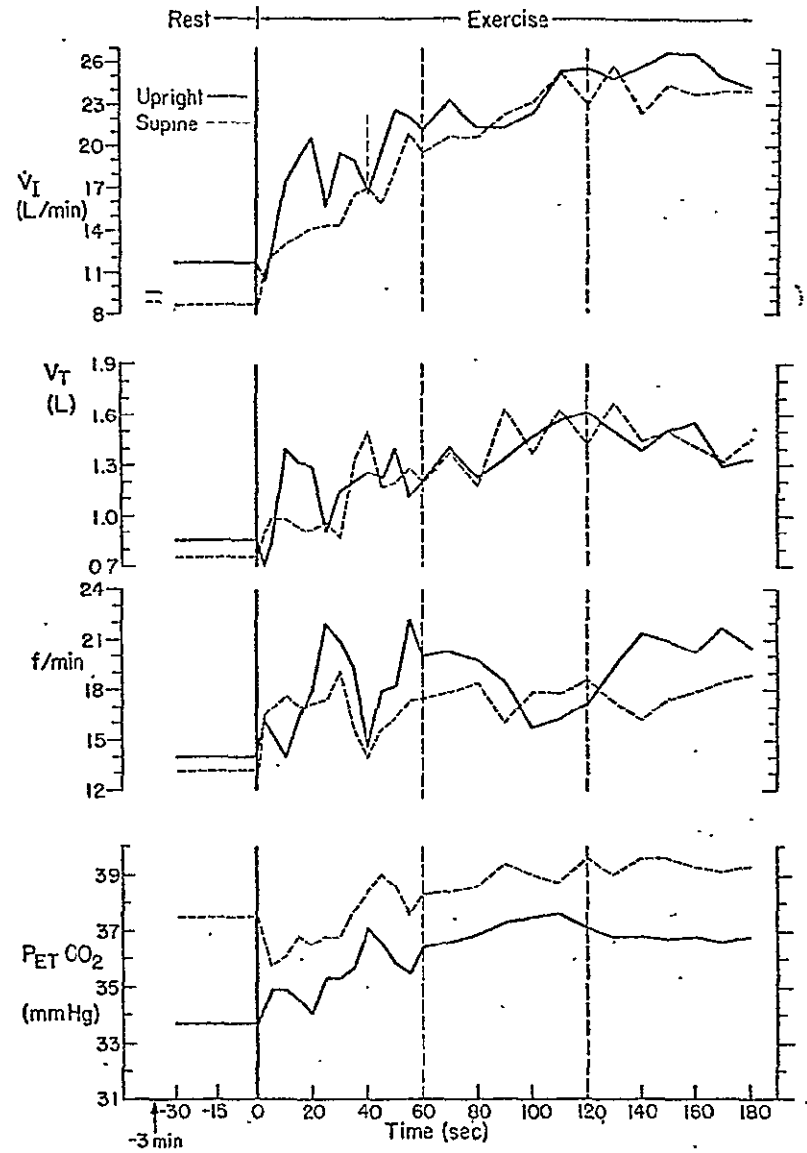


Fig 3. Inspired ventilation ($\dot{V}_I$), tidal volume (V_T), frequency (f), and end-tidal CO_2 pressure ($P_{ET}CO_2$) corresponding to Fig 1 in time.

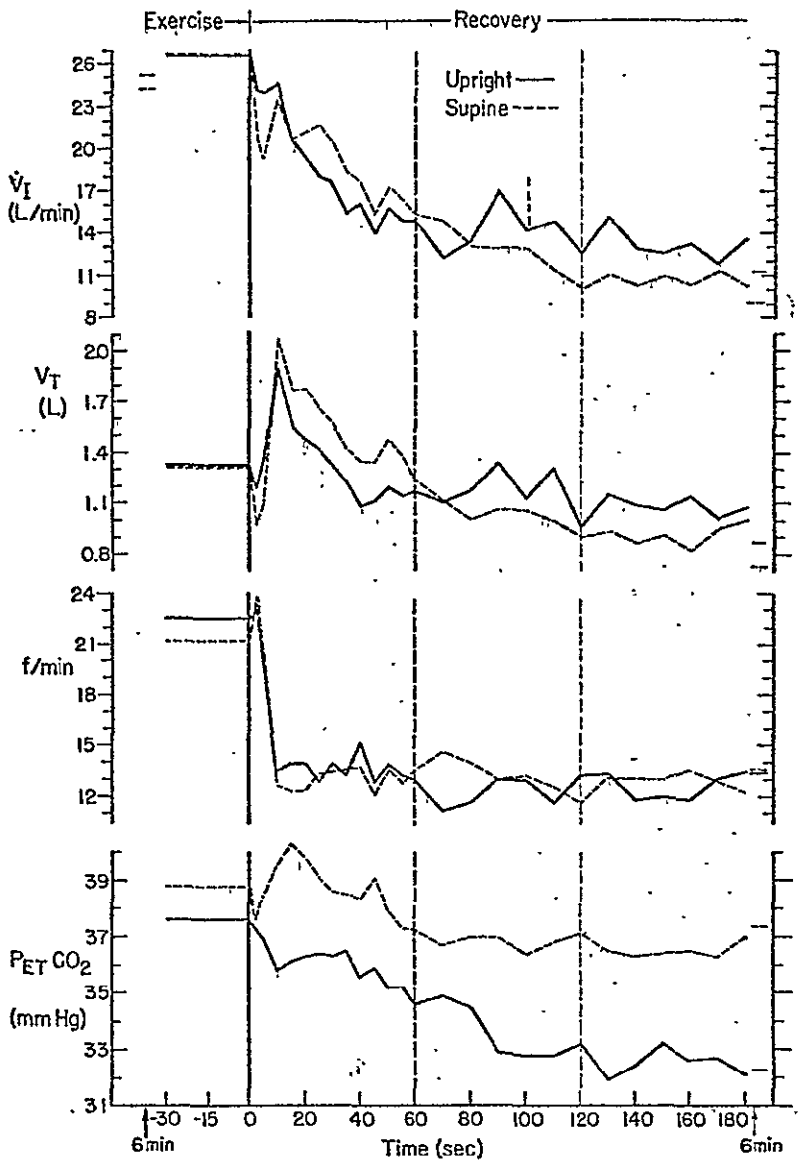


Fig 4. Same as Fig 3 corresponding to Fig 2 in time.

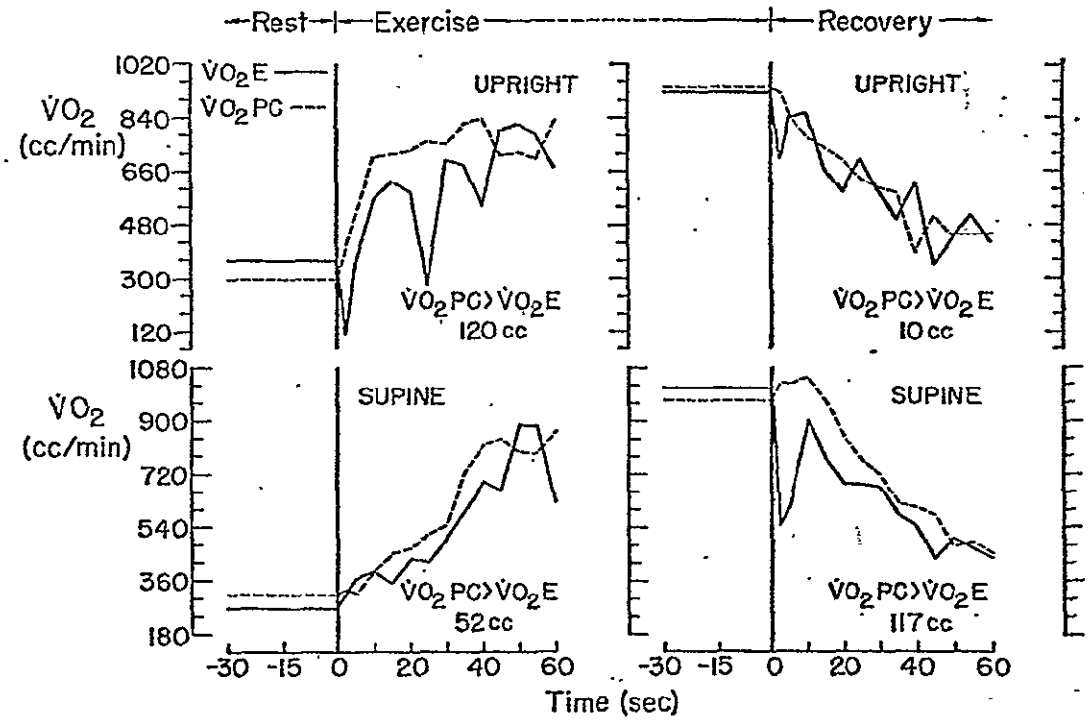


Fig 5. O_2 intake by the lungs and pulmonary capillaries during the first min of exercise and recovery. When $\dot{V}O_2PC$ exceeds $\dot{V}O_2E$ then lung O_2 stores are depleted. The amount of O_2 lost is estimated from the area between the curves.

Table 1. Physical Characteristics and Aerobic Power of Subjects.

Subject	Age (yr)	Ht (cm)	Wt (kg)	$\dot{V}O_2$max (L/min)
1	29	183	65.6	2.69
2	45	176	79.9	3.23
3	34	183	82.7	3.18
4	31	170	76.0	2.64
5	47	190	77.2	2.59
6	32	174	74.7	2.33
Mean	36.3	179	76.0	2.78
S.D.	7.7	7	5.9	0.35

Table 2. Mean steady state values for HR and respiratory variables for 6 subjects in the upright (U) and supine (S) posture 3 min before and 5 min after exercise and recovery.

		$\dot{V}O_2$ (cc/min)	R	$\dot{V}_I$ (L/min)	$\dot{V}_I/\dot{V}O_2$	$P_{ET}CO_2$ (mmHg)	HR (per min)
Before	U	294	.77	9.54	32.9	33.1 **	76 *
	S	295	.80	8.80	29.9	36.3	63
Exercise	U	952	.82	25.15	26.5	38.3	96
	S	967	.82	24.15	25.0	39.6	93
Recovery	U	312	.86	11.22	35.9	32.3 *	83 **
	S	282	.88	9.09	32.3	37.4	66

* $p < .05$

** $p < .01$

$\dot{V}O_2$: O_2 consumption by Douglas bag; R: respiratory exchange ratio; $\dot{V}_I$: ventilation; $\dot{V}_I/\dot{V}O_2$: ventilation equivalent for O_2; $P_{ET}CO_2$: end-tidal CO_2 pressure; HR: heart rate.

Table 3: Differences in pulmonary capillary O_2 transfer ($\dot{V}O_2PC$), ventilation and heart rate between upright (U) and supine (S) posture during first 40 sec of exercise and first 100 sec of recovery.

	EXERCISE Upright - Supine (0 sec-40 sec)			RECOVERY Upright - Supine (0 sec-100 sec)		
Subject	$\Delta\dot{V}O_2PC$ (cc)	$\Delta\dot{V}_I$ (L)	ΔHR (per min)	$\Delta\dot{V}O_2PC$ (cc)	$\Delta\dot{V}_I$ (L)	ΔHR (per min)
1	245	3.48	9	- 31	8.93	-13
2	109	0.75	16	-158	-1.12	-24
3	98	0.92	30	-244	-0.87	-33
4	98	3.38	12	-198	-7.86	-22
5	104	1.20	5	-147	-2.36	-16
6	160	2.88	3	-135	-0.11	11
Mean	136	2.10	13	-152	-0.57	-16
S.D.	58	1.28	10	72	5.43	15
p	$<.005$	$<.02$	$<.05$	$<.005$	NS	$<.05$

Values for $\Delta\dot{V}O_2PC$ represent the area between the curves for U and S from Figs 1 and 2 and $\Delta\dot{V}_I$ values were obtained similarly from Figs 3 and 4. Symbols as in Table 2.

PART III

FORCED OSCILLATIONS WITH AIR AND HELIOX TO DETERMINE SITE OF AIRWAY OBSTRUCTION

ABSTRACT

A modified forced oscillation (FO) method for determining total respiratory conductance (TRC), as reported previously, was used to assess density dependence of airflow and thence the predominant site of flow limitation in patients with various types of obstructive lung diseases. The rationale for this procedure is that turbulent flow is density dependent, whereas laminar flow is not. Normally 80% of total airway resistance is generated in larger airways, where flow is turbulent and only 20% in smaller airways with predominantly laminar flow. When the obstructive process is located in the smaller airways the laminar component will increase and flow will be less affected by changes in gas density. TRC was measured breathing air and Heliox (80% He, 20% oxygen) on 25 healthy normals and 41 patients who all had routine pulmonary function tests. TRC was corrected for volume (TRC/FRC) and compared with maximal mid-expiratory flow (MMEF) corrected for volume (MMEF/VC) as an index of obstructive impairment. The correlation between TRC/FRC and MMEF/VC while breathing air was highly significant ($r = .64$; $p < .0001$). Mean values for TRC/FRC and MMEF/VC were significantly lower in the patients than in the normals but the mean response to Heliox was only slightly less. Further analysis of the data showed that the response to Heliox is not closely related to the severity of the disease. About equal numbers of the most severely obstructed patients responded well to Heliox as did not. It is concluded that the Heliox test with the FO method provides additional information as to the site of flow limitation either in the central or peripheral airways regardless of the degree of obstruction. This may be a valuable adjunct for the prognosis as well as for a more specific treatment of the disease.

INTRODUCTION

The sine-wave forced oscillation (FO) technique for studying respiratory mechanics, originally introduced by DuBois et al. (6), has been modified for application as a screening test for detecting and quantitating obstructive airway disease as reported previously (9). More recently the feasibility of determining the predominant site of flow limitation, either in the peripheral or proximal airways, has been explored by measuring pressure and flow during FO breathing air and Heliox (80% He, 20% O_2). The rationale underlying this procedure is that flow increases for a given pressure head when air is replaced by a gas of lower density in a system where the flow regime is turbulent, but not when it is laminar. In the healthy mammalian lung about 80% of total airway resistance is located in the medium size and larger airways, where flow is turbulent, whereas the small airways with less than 2 mm diameter, where flow is predominantly laminar, contribute a relatively small fraction (8). Therefore in normal individuals airflow is demonstrably density dependent. However, when obstructive impairment originates in the peripheral airways and contributes increasingly to the overall flow limitation, the response to changes in density will be correspondingly reduced. This concept has been used to localize the site of airway obstruction in asthma by measuring maximum forced expiratory flow breathing air and a helium mixture (4) and to demonstrate obstruction in smaller airways in smokers (5). In a preliminary study from this laboratory (10) it was reported that the measurement of total respiratory conductance (TRC) by the FO method is highly sensitive to changes in density and the purpose of the present investigation was to determine whether this method is suitable for detecting the predominant site of flow limitation in a larger number of patients in whom the presence and severity of their obstructive impairment had been established by FO and other ventilatory tests.

The practical importance of identifying the site of obstruction is evident not only for diagnostic reasons but also from the therapeutic and prognostic point of view.

METHODS AND PROCEDURES

The apparatus used to measure total respiratory resistance (TRR) or its reciprocal, total respiratory conductance (TRC) by forced oscillation (FO) was similar to that described earlier (10). The modifications designed to permit switching from air to Heliox are incorporated in the scheme shown in Fig 1. Forced oscillations are generated by a specially designed reciprocating pump with constant stroke volume and frequency. The stroke volume is adjustable from 15-45 ml

and the frequency from 2-17 cps. The advantage of the pneumatic pump over the low frequency loudspeaker used previously to generate sine-wave FOs is that volume displacement and therefore flow rate is constant for a given frequency and stroke volume at corresponding points in the cycle, regardless of the physical characteristics of the gas. Thus changes in pressure amplitude directly reflect changes in TRR and its reciprocal TRC. The subject wearing a nose-clip (Fig 1) breathes quietly through a plastic tube (ID: 3 cm, 20 cm long) attached at the opposite end to the pump (Luftpumpe), with a Fleisch No. 2 pneumotachograph interposed midway. A constant bias flow of 0.5 liters/sec is drawn through the system to avoid rebreathing. The length of bore of the tubing for the bias flow is chosen so that it provides low impedance at low frequencies (breathing) and high impedance at high frequencies (FO). A check valve is inserted upstream of the inspiratory port at the mouth to avoid expiratory backlash. The pneumotachograph is attached to a differential pressure transducer (Validyne, Model MP45, range $\pm$ 2 cm H_2O) and the output of its amplifier displayed on the y-axis ($\dot{V}$) of an oscilloscope (Tektronix 502). Another transducer of the same model (range $\pm$ 10 cm H_2O) records the differential pressure (P) between the inside of the tube at the mouth and ambient pressure. The pressure is displayed on the x-axis of the oscilloscope. Filter circuits incorporated in the Validyne transducer indicators (CD12) are used to eliminate frequencies above 10 cps. The heated pneumotachograph was calibrated on air regularly with a precision Rotameter and the sensitivity adjusted to provide a deflection of 5 cm/liter/sec on the screen. The pressure record was calibrated by water manometer to give a deflection of one cm/cmH_2O. After the subject has breathed through the system for several minutes he holds his hands to his cheeks to minimize flutter. Then the frequency of the pump is adjusted to close the $\dot{V}/P$ loop on the screen at the individuals resonant frequency, where the phase difference between $\dot{V}$ and P approaches zero. The $\dot{V}/P$ angle is noted on a rotating translucent template to calculate TRC_{air}. Since TRC is volume dependent, measurements are made as close to the end-tidal level (functional residual capacity) as possible, and to correct for inter-individual differences in lung volume each subject's TRC was divided by his residual volume to obtain the "specific respiratory conductance" (SRC). The FRC was measured by the nitrogen-washout method as part of the standard pulmonary function tests performed on all subjects. After obtaining the TRC on air the subject was switched to Heliox and took three maximal breaths (vital capacity) before the next measurement for TRC_{He}.

The effect of the low-density gas was expressed in terms of:

$$\Delta\%SRC = \frac{SRC_{He} - SRC_{air}}{SRC_{air}} \times 100$$

The other ventilatory tests included total lung capacity and its subdivisions by direct and indirect spirometry (nitrogen-washout) and the maximal flow-volume loop recorded with a WEDGE spirometer on an x-y recorder (Sanborn, Model 670-400A) before and after bronchodilator. The maximal mid-expiratory flow (MMEF) was chosen as the most sensitive routine test for overall airway obstruction. The MMEF was divided by the individual's vital capacity (MMEF/VC) to correct for volume dependence.

The 41 patients selected for the study had been referred to our laboratory for routine pulmonary function tests with the clinical diagnosis of chronic obstructive lung disease and were accepted regardless of the duration, type or severity of their ailment. Twenty-five asymptomatic volunteers served as normal subjects. None of them had any indication of respiratory disease in their medical history. There were 11 smokers and 14 nonsmokers among the normals, whereas 33 (80%) of the patients were or had been smokers. The normals were on the average considerably younger than the patients (see Table 1).

RESULTS AND DISCUSSION

Individual data on all 66 subjects are presented in Table 1. Of the 25 asymptomatic volunteers none had an MMEF/VC of less than .50, which is considered the lower limit of the normal range in this laboratory. Therefore this group can be accepted as free of obstructive impairment of any kind. Among the patients only 6 (15%) had an MMEF/VC of more than .50, thus 85% had a significant obstructive defect. Bronchodilator (Isuprel) was administered by vaporizer to 36 of the 41 patients. Of these 11 (31%) showed no response, 25 (69%) had a positive response with 16 (64%) of them improving their MMEF/VC by more than 50%. By this evidence an appreciable number had an at least partially reversible type of obstruction.

Mean values for MMEF/VC, SRC_{air} and $\Delta\%SRC_{He\text{-}air}$ for the normals and patients are shown in Table 2. In the patients MMEF/VC and SRC_{air} were significantly less than in the normals and the response to Heliox was lower in the former than the latter, but the difference was barely statistically significant. This suggests that the response to Heliox is not closely related to the presence or degree of airway obstruction. Indeed, when correlations were calculated be-

tween either MMEF/VC or SRC_{air} and the response to Heliox in percent for all 66 subjects, no significant correlations were found. This is in good agreement with the results reported by Despas et al. (4) on patients with asthma and chronic bronchitis. Of 27 asthmatic patients with significant obstruction 13 responded well to Heliox and 11 showed little or no response. Similarly a study by Antic and Macklem (7) reported that of 48 asthmatic patients 56% showed an increase in MMEF of more than 20% breathing Heliox (responders) and 44% less than 20% (non-responders). These authors concluded that the main site of airway obstruction in asthmatics may be in small airways (non-responders) or large airways (responders). But they emphasize that the preservation of a response to Heliox in the presence of airway obstruction does not exclude narrowing of small airways, but indicates that larger airways are involved to greater extent than when the response to low density gas is minimal. Their data on asthmatics suggest that without a history of smoking, chronic bronchitis or repeated respiratory infections, narrowing is predominantly in central airways, while it is more likely to be in peripheral airways in the presence of these complicating factors. Benetar and associates (2) also express the opinion that a poor response to helium in asthma reflects the presence of an underlying non-reversible component of obstructive disease, and these patients usually show little improvement in long-term follow-up studies. In another study also on asthmatic patients Chan-Yeung et al. reported that 22 out of 27 patients responded to helium with an increase in MMEF/VC of more than 20% suggesting that in most of their patients the site of obstruction was in the larger airways. All of these patients were in remission and most of them had only a mild degree of obstruction. Moreover, only one case was complicated by chronic bronchitis.

Our unselected group of patients with obstructive disease included many cases with chronic bronchitis and emphysema as well as asthmatics and therefore represents a wider variety of airway pathology. When all 66 subjects were divided into two equal groups according to whether their SRC_{air} was above, (Group A, Table 3) or below (Group B) the median SRC (0.091), the average response to Heliox was slightly higher in the more obstructed group B, but the difference was not statistically significant. This is a corollary to the earlier observation that there is no close correlation between the degree of obstructive disease and density dependence of airflow. In order to ascertain the distribution of good responders and poor responders to Heliox among the less obstructed (A) and more

obstructed patients (B) the number of cases whose response was above the median $\Delta\%SRC_{He-air}$ (65%) for all subjects (I) or below it (II) was determined and the mean values for each of the four groups are shown in Table 4. It is noted that there are about equal numbers of good and poor responders in both the less severely (A) and more severely (B) obstructed groups. The implications are that the predominant site of airway narrowing can be either in the smaller or the larger airways regardless of the severity of the obstruction. Another striking feature is that the contrast between good (BI) and poor (BII) responders in the more obstructed group is much greater than in the less obstructed patients (AI vs AII) as far as density dependence of airflow is concerned. It is possible that the Heliox test is able to localize the site of airway narrowing more readily in patients with severe obstruction than in those with less disturbance. The mean $\Delta\%SRC$ for the good responders in the more severely obstructed group (BI) was considerably higher (91%) than the mean for the normal subjects (74%) in Table 2. Thus apparently airflow in some patients with severe obstruction predominantly in the larger airways may be even more density dependent than in healthy people.

MMEF and SRC_{air}

The measurement of MMEF obtained from the maximal flow volume loop and SRC_{air} by the FO method have both been used as an index of obstructive impairment in this study. There was a highly significant correlation between the two when the data on all 66 were combined ($r = .64$; $p < .0001$). Table 3 also shows good agreement between the two criteria of airflow in that the mean difference between the 33 less obstructed individuals (A) and the more severely affected ones (B) was proportionately the same.

However, when group A and B were separated according to their response to Heliox, (Table 4) the good responders (I) showed slightly higher mean values for MMEF than the poor responders (II) in both Group A and B, whereas there was no difference in SRC_{air} between AI and AII and in Group B the poor responders (BII) had a slightly higher SRC_{air} than the good responders (BI). Apparently under certain circumstances the results obtained from the MMEF may indicate more obstruction than by FO. The former involves a forced expiratory effort after maximal inspiration and is apt to cause dynamic compression of the airways, particularly in patients with reduced pulmonary compliance as in many cases of emphysema. This causes more pronounced narrowing of the airways than would occur without the maximal expiratory effort. The FO method which is performed

during quiet breathing does not drastically change the transmural pressures in the airways as the MMEF does and therefore will not reflect a tendency for dynamic compression that may be present. Of the 16 patients in group BII, 11 had a sharp inflection in their expiratory flow-volume loop typical for dynamic compression (Fig 2) and also had a grossly enlarged residual volume characteristic of emphysema.

This is the first time, to our knowledge, that density dependence of airflow has been determined by the FO method. Several other investigations have used maximal flow-volume loops taking the change in MMEF as a measure of the response (1, 2, 3, 4, 5). With this method the average increase in flow with helium is between 40 and 50% in healthy subjects, while it was considerably higher (74%) with the FO method in the present study. For this reason the determination of Δ%SRC by FO may be a more sensitive tool for testing density dependence of airflow. It is possible that the FO procedure in itself modifies the flow regime in the airways in some way that increases the turbulent component and thus the response to helium.

CONCLUSIONS

The FO method as used in this study compares favorably with other methods for evaluating obstructive airway disease, it requires minimal cooperation and effort on the part of the patient which makes it particularly suitable for small children and debilitated patients as well as for screening purposes in epidemiological studies. Repetition of the test using Heliox gives additional information on the predominant site of obstruction in smaller or larger airways, thereby revealing clues for differential diagnosis that are not apparent from standard pulmonary function tests. With regard to therapy the localization of the bronchoconstriction may gain increasing importance since it has been shown that different bronchodilating agents have preferential effects on certain segments of the bronchial system. In a recent study by Ingram et al. (7) atropine, which blocks postganglionic cholinergic neural pathways, appeared to have a preferential effect on larger airways while isoproterenol, which affects bronchial smooth muscle directly by beta adrenergic stimulation, seems to act more selectively on smaller, peripheral airways.

REFERENCES

1. Antic, R. and P.T. Macklem. The influence of clinical factors on the site of airway obstruction. Amer. Rev. Resp. Dis. 114:851-859, 1976.

2. Benetar, S.R., T.J.H. Clark and G.M. Cochrane. Clinical relevance of the flow rate response to low density gas in asthmatics. Amer. Rev. Resp. Dis. 111:126-134, 1975.

3. Chan-Yeung, M., R. Abdoud, M.S. Tsao and L. Maclean. Effect of helium on maximal expiratory flow in patients with asthma before and during induced bronchoconstriction. Amer. Rev. Respir. Dis. 113:433-443, 1976.

4. Despas, P.J., M. LeRoux and P.T. Macklem. Site of airway obstruction in asthma determined by measuring maximal expiratory flow breathing air and helium-oxygen mixtures. J. Clin. Invest. 51:3235-3243, 1972.

5. Dosman, J., F. Bode, J. Urbanetti, R. Martin and P.T. Macklem. The use of a helium-oxygen mixture during maximum expiratory flow to demonstrate obstruction in small airways in smokers. J. Clin. Invest. 55:1090-1099, 1975.

6. DuBois, A.B., A.W. Brody, H. Lewis and B.F. Burgess, Jr. Oscillation mechanics of lungs and chest in man. J. Appl. Physiol. 8:587-594, 1956.

7. Ingram, R.H., Jr., J.J. Wellman, E.R. McFadden, Jr. and J. Mead. Relative contributions of large and small airways to flow limitation in normal subjects before and after Atropine and Isoproterenol. J. Clin. Invest. 59: 696-703, 1977.

8. Macklem, P.T. and J. Mead. Resistance of central and peripheral airways measured by a retrograde catheter. J. Appl. Physiol. 22:395-401, 1967.

9. NASA Contract NAS9-12572. Specialized physiological studies in support of manned space flight. Report February, 1973, Part E: The use of the forced-oscillation method to determine total respiratory conductance in healthy subjects and pulmonary patients.

10. NASA Contract NAS9-14472. Specialized physiological studies in support of manned space flight. Report February, 1976, p. 62-74. Total respiratory conductance by the forced oscillation method using air and Heliox as a screening test. A pilot study.

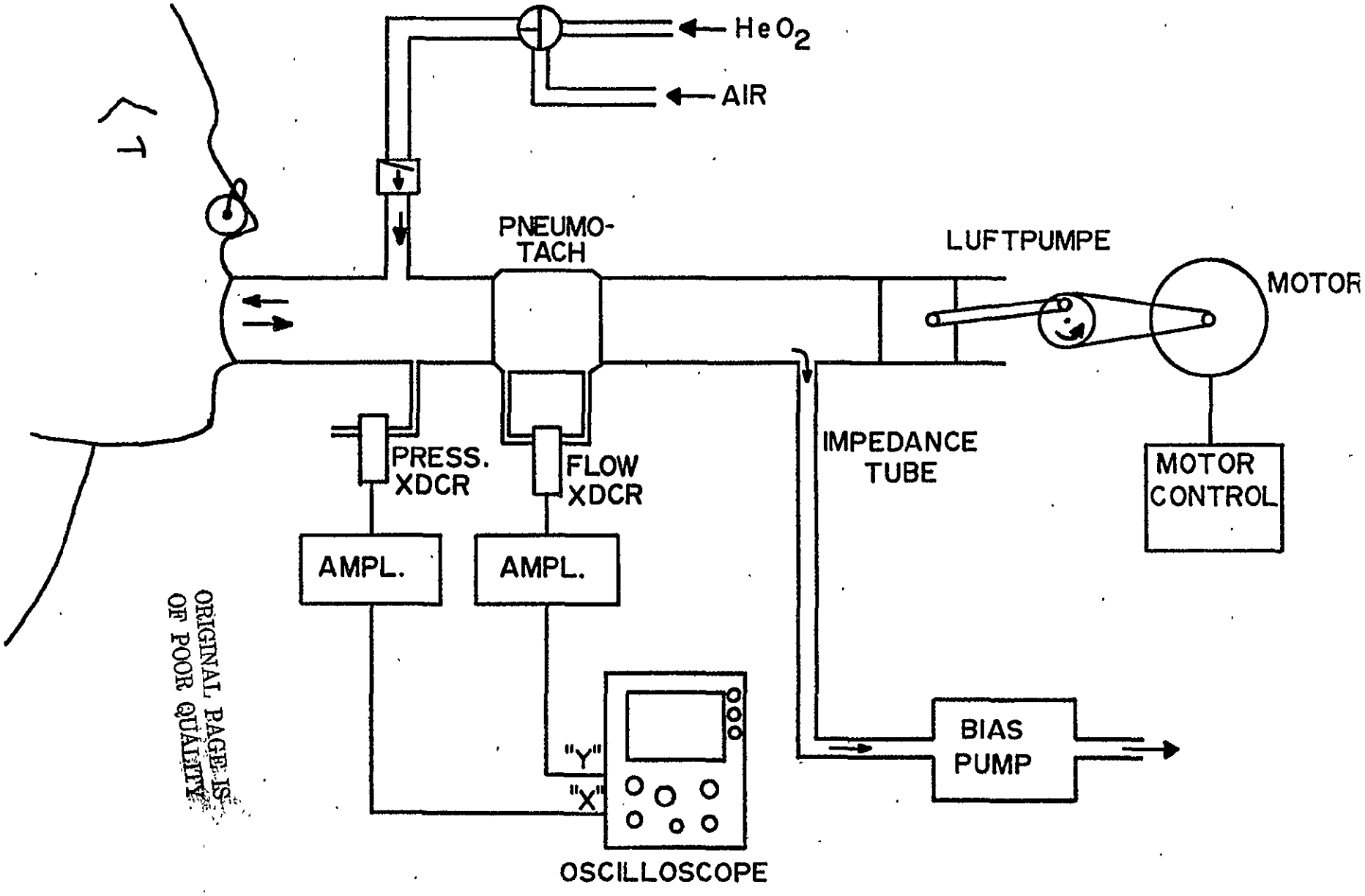


Figure 1. Forced oscillation system for measuring total respiratory conductance and density dependence of airflow.

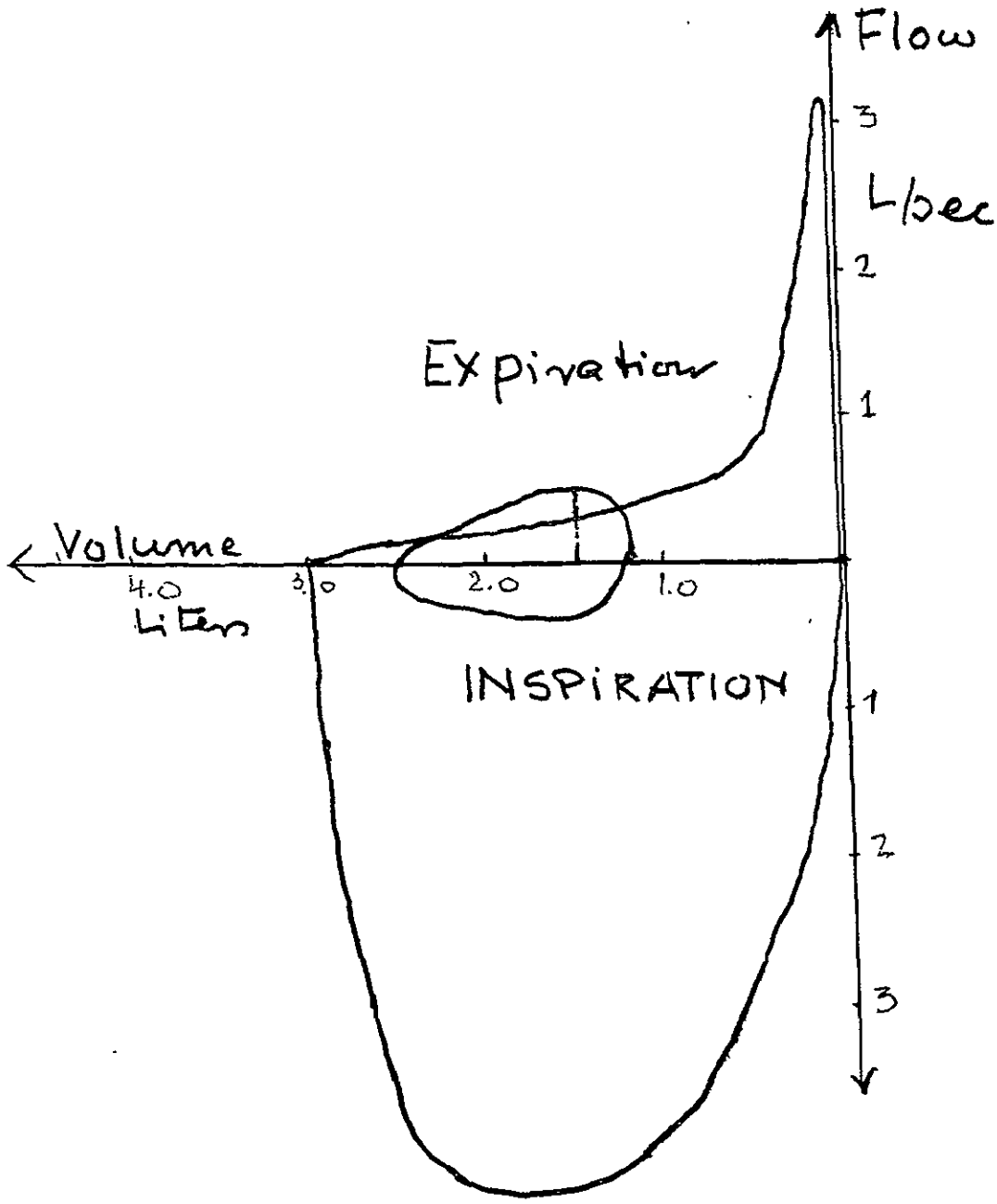


Figure 2. Forced flow volume loop of a patient with advanced emphysema with a record of spontaneous breathing superimposed at the same volume. Note sharp expiratory inflection in the forced VC typical for dynamic compression. Spontaneous flow exceeds that of MMEF.

TABLE 1

Subject No.	Sex	Age (yr)	Ht (cm)	Wt (kg)	FRC (l)	VC (l)	MMEF (l/sec)	MMEF/ VC	SRC-Air: TRC/FRC	SRC-He: TRC/FRC	Δ (He-Air)	Δ %
						PATIENTS						
1	M	31	179	69.0	3.75	6.22	3.00	0.48	.112	.177	.065	58
2	M	65	180	81.5	3.99	4.73	1.52	0.32	.107	.145	.038	36
3	M	47	173	65.0	4.42	4.79	1.07	0.22	.075	.125	.050	67
4	F	56	156	39.5	2.62	1.71	0.33	0.19	.078	.135	.057	73
5	M	81	165	58.0	2.21	2.11	0.50	0.24	.126	.186	.060	48
6	M	71	177	63.5	5.97	1.74	0.17	0.10	.033	.060	.027	82
7	M	47	182	76.0	4.20	4.96	4.08	0.82	.089	.126	.037	42
8	F	39	152	78.3	2.88	1.85	0.69	0.37	.071	.105	.034	48
9	F	66	168	51.0	3.08	2.23	0.32	0.14	.098	.130	.032	33
10	M	59	179	82.0	4.17	4.46	2.00	0.45	.096	.153	.057	59
11	F	44	165	49.5	3.83	3.90	1.77	0.45	.101	.167	.066	65
12	F	53	173	56.4	3.70	2.20	0.19	0.09	.048	.088	.040	83
13	F	28	163	57.0	3.17	4.34	3.46	0.80	.118	.194	.076	64
14	M	39	169	114.5	1.64	4.76	3.00	0.63	.205	.262	.057	28
15	F	73	157	64.5	3.57	1.41	0.08	0.06	.067	.138	.071	105
16	M	48	183	78.6	5.53	2.78	0.46	0.17	.063	.072	.009	14
17	M	70	173	56.8	4.82	3.13	0.62	0.20	.070	.123	.053	43
18	M	67	180	74.5	3.82	4.35	2.12	0.49	.071	.105	.034	48
19	M	46	179	102.7	3.11	5.14	2.00	0.39	.077	.133	.056	73
20	M	55	177	73.0	2.10	1.77	0.48	0.27	.119	.211	.092	77
21	M	56	174	96.0	6.18	2.39	0.31	0.13	.058	.080	.022	38
22	M	64	172	76.0	5.83	2.67	0.25	0.09	.032	.050	.018	56
23	F	64	155	79.3	2.13	1.47	0.48	0.33	.117	.201	.084	72
24	M	42	173	53.0	3.98	4.48	1.68	0.38	.090	.133	.043	48
25	M	46	178	61.4	3.55	4.67	1.08	0.23	.068	.121	.053	78
26	M	61	179	64.0	5.91	5.37	0.75	0.14	.053	.081	.028	53
27	M	57	176	71.0	7.03	2.91	0.20	0.07	.044	.072	.028	64
28	M	79	182	72.0	1.99	1.77	0.67	0.38	.073	.151	.078	107
29	M	51	179	73.0	5.94	2.73	0.33	0.12	.040	.060	.020	50
30	F	55	163	76.0	2.58	2.80	2.24	0.87	.112	.239	.127	114

TABLE 1 (continued)

Subject No.	Sex	Age (yr)	Ht (cm)	Wt (kg)	FRC (l)	VC (l)	MMEF (l/sec)	MMEF/ VC	SRC-Air TRC/FRC	SRC-He TRC/FRC	Δ (He-Air)	Δ %
PATIENTS (continued)												
31	M	60	181	63.6	5.07	4.16	0.58	0.14	.091	.121	.030	33
32	M	60	169	71.8	4.29	3.00	0.75	0.25	.070	.119	.049	70
33	M	60	177	73.2	5.23	2.57	0.42	0.16	.034	.060	.026	76
34	M	68	170	73.0	5.48	3.10	0.24	0.08	.031	.070	.039	126
35	F	57	164	92.5	2.72	2.18	0.92	0.42	.051	.078	.027	53
36	M	59	183	82.0	4.43	2.43	0.29	0.12	.056	.076	.020	36
37	M	64	170	83.5	3.67	1.92	0.64	0.33	.033	.060	.027	82
38	M	60	175	81.0	5.12	2.74	0.92	0.34	.025	.149	.024	96
39	M	54	180	92.0	3.41	4.29	1.38	0.32	.082	.106	.024	29
40	F	61	160	68.0	1.89	2.26	1.79	0.79	.132	.191	.059	45
41	M	48	175	85.0	3.37	5.19	3.67	0.71	.100	.158	.158	58

TABLE 1 (continued)

Subject No.	Sex	Age (yr)	Ht (cm)	Wt (kg)	FRC (l)	VC (l)	MMEF (l/sec)	MMEF/ VC	SRC-Air TRC/FRC	SRC-He TRC/FRC	Δ (He-Air)	Δ %
						ASYMPTOMATIC VOLUNTEERS						
1	M	31	174	71.9	2.29	5.00	5.38	1.08	.149	.280	.131	88
2	F	50	164	63.5	2.57	3.35	4.46	1.33	.173	.292	.119	69
3	F	29	170	72.5	3.13	3.92	5.13	1.31	.114	.190	.076	67
4	M	37	185	63.0	3.95	5.72	3.17	0.55	.091	.136	.045	49
5	M	33	183	82.5	2.87	4.68	3.56	0.76	.070	.149	.079	113
6	M	35	184	88.0	2.27	5.02	6.62	1.32	.179	.276	.097	54
7	M	30	188	81.0	3.73	6.69	5.85	0.87	.119	.167	.048	40
8	M	45	180	63.8	3.73	5.58	3.41	0.61	.160	.208	.048	30
9	M	28	183	63.9	4.47	5.75	3.23	0.56	.095	.137	.042	44
10	M	45	176	68.1	2.89	5.16	4.93	0.96	.122	.211	.089	73
11	M	28	173	59.9	3.00	5.39	3.92	0.73	.113	.180	.067	59
12	M	29	185	89.3	3.38	6.26	4.70	0.75	.043	.085	.042	98
13	M	29	173	76.7	3.26	5.78	3.19	0.55	.117	.203	.086	74
14	M	26	184	82.5	3.34	5.13	2.74	0.53	.073	.152	.079	108
15	M	37	174	63.9	2.67	4.69	4.77	1.02	.115	.245	.130	113
16	M	34	195	116.4	2.44	5.51	3.85	0.70	.121	.192	.071	59
17	M	27	168	59.6	2.65	5.21	4.15	0.80	.112	.180	.068	61
18	M	28	175	63.9	2.48	4.48	5.23	1.17	.107	.203	.096	90
19	M	32	174	73.3	1.88	4.33	3.41	0.79	.184	.309	.125	68
20	F	53	165	62.5	2.78	4.15	5.25	1.27	.084	.169	.085	101
21	F	21	184	54.0	2.80	4.35	2.37	0.54	.128	.215	.087	68
22	M	33	178	87.6	2.28	5.44	4.37	0.80	.119	.223	.104	87
23	M	28	175	75.5	2.32	5.31	4.31	0.81	.153	.253	.100	65
24	M	23	183	84.0	2.62	5.69	4.02	0.71	.101	.195	.094	93
25	M	42	173	75.5	3.21	4.83	2.78	0.58	.094	.178	.084	89

FRC: Functional residual capacity; VC: Vital capacity; MMEF: Maximal midexpiratory flow; TRC: Total respiratory conductance; SRC: Specific respiratory conductance = TRC/FRC.

TABLE 2

	n	MMEF/VC	SRC_{air}	$\Delta\%SRC_{He-air}$
Normals	25	0.84 (0.27)	0.117 (0.035)	74% (23%)
Patients	41	0.32 (0.23)	0.078 (0.035)	62% (25%)

TABLE 3

A	$SRC_{air} > 0.091$	33	0.670 (0.287)	0.125 (0.028)	65% (21%)
B	$SRC_{air} \leq 0.091$	33	0.330 (0.262)	0.062 (0.020)	68% (28%)

TABLE 4

A	$SRC_{air} > 0.091$				
	I $\Delta\%SRC > 65\%$	15	0.76 (0.31)	0.125 (0.025)	83% (15%)
	II $\Delta\%SRC \leq 65\%$	18	0.63 (0.27)	0.125 (0.031)	50% (13%)
B	$SRC_{air} \leq 0.091$				
	I $\Delta\%SRC > 65\%$	17	0.37 (0.31)	0.058 (0.020)	91% (18%)
	II $\Delta\%SRC \leq 65\%$	16	0.28 (0.21)	0.066 (0.019)	44% (12%)

Mean values and standard deviations in parenthesis for MMEF/VC: maximal midexpiratory flow divided by vital capacity; SRC_{air}: Specific respiratory conductance and ΔSRC_{He-air}: The difference in percent between SRC_{He} and SRC_{air}.

Table 2: Normals and unselected patients.

Table 3: All subjects were divided into Group A with SRC_{air} above the median (SRC = .091) and Group B, below the median.

Table 4: The subjects with $\Delta\%SRC_{He-air}$ above the median for all (65%) and those below the median were separated (good responders: I, poor responders: II) for Group A and B respectively.

PART IV

A NEW METHOD FOR DETERMINING CLOSING VOLUME USING FORCED OSCILLATIONS

ABSTRACT

A new method is described for measuring closing volume (CV) as a test for obstructive disease in the airways. The procedure uses forced oscillations to measure total respiratory resistance during a slow vital capacity maneuver. Beginning airway closure is indicated by a sudden increase in resistance. This method was compared with the accepted single breath N_2 test by using both simultaneously. Paired comparison of the results on 30 patients and normal subjects indicate that there is no significant difference in the values obtained for CV by either method and the correlation between the two was highly significant. The reproducibility of the two methods is about the same. In 10% of the cases CV could not be determined by the N_2 test but was readily apparent by the FO method. These were cases with advanced obstructive disease. The FO method dispenses with the use of O_2, so that repeated measurements can be made within a few minutes.

INTRODUCTION

The closing volume (CV) is that lung volume at which airways begin to close in the dependent zones of the lung (2). This point can be determined by plotting the nitrogen concentration in the expired air after a single maximal inspiration of 100% O_2 from residual volume, against the expired vital capacity. Toward the end of expiration the dependent airways begin to close and the nitrogen in the expirate rises with a greater contribution coming from the upper zones of the lung, which have received less O_2 during inspiration. The CV test has been advocated as a simple means of detecting early stages of bronchial pathology, particularly in smokers (3) and has been used extensively in this laboratory for a number of years (4).

Experience has shown that the precise identification of the CV is not always possible, when the change in slope from phase 3 to phase 4 is equivocal. This is frequently the case in patients with significant obstructive disease. It appeared that a simultaneous recording of total respiratory resistance by the forced oscillation (FO) method (see Part III of this report) might facilitate the identification of the CV, because closure of a certain number of airways must reduce the effective cross-sectional area of the system and increase resistance. The present study was designed to combine the established method (CV_{N2}) with the forced oscillation method (CV_{FO}) on the same record to see whether any appreciable changes in resistance occur where the N_2 record indicates the CV.

METHODS AND PROCEDURES

The arrangement of the equipment used to perform the combined procedure is shown in Fig 1. The subject wearing a nose clip seals his lips around a plastic tube (ID: 3 cm; 20 cm long) attached at the opposite end to a reciprocating constant volume displacement (40 ml) pump creating sine wave oscillations at approximately 5 cps. On a signal the subject exhales maximally while the inspiratory port is switched to pure O_2 of which the subject inhales a full vital capacity. During the following controlled, slow exhalation to his residual volume a continuous record is obtained of 1) Exhaled N_2 concentration from the sampling line at the mouth with a Nitralyzer (MedScience) recorded on one y-axis of an x-y recorder (Hewlett-Packard #7046A). 2) The amplitude of pressure oscillations close to the mouth with a Validyne pressure transducer (Model MP45) recorded on a second channel on the y-axis. 3) Volume expired obtained by integrating the signal from a Fleish

(No. 2) pneumotachograph with another Validyne transducer and amplifier on the x-axis of the recorder. Thus both pressure and nitrogen records are coordinated with volume. Since the displacement of the pump is constant, the flow amplitude is also constant and the pressure amplitude displayed on the record is directly proportional to total respiratory resistance and inversely to the conductance. Since the same frequency of oscillations was used on all subjects and was not attuned to the resonant frequency of the lungs and chest for each individual, the pressure record, strictly speaking, represents total impedance rather than resistance. However changes in compliance and inertance were considered negligible under these circumstances. This arrangement permits direct observation of changes in pressure patterns and their relation to the CV indicated by the N_2 record.

RESULTS AND COMMENTS

A total of 33 subjects were tested with the combined procedure for CV, each performing at least two tests. There were 15 patients chosen at random from those reporting to the pulmonary function laboratory for routine procedures and 18 healthy volunteers. Closing volumes could be identified by both methods in 30 individuals (Table 1), whereas the N_2 record did not indicate a CV in the remaining three. One of these was a young healthy subject, the other three were patients with advanced chronic obstructive disease (see below).

The record reproduced in Fig 2 belongs to a 30 year old healthy female non-smoker. The pressure amplitude at the mouth generated by the FO pump is shown above and the N_2 record below on the ordinate against volume on the abscissa. The N_2 record describes the four phases typical of the single breath CV test as described by Dollfuss et al. (1). The onset of phase four is characterized by a sharp rise in N_2 concentration at the very end of expiration. It is interesting to see that the pressure amplitude of FO shows a marked increase closely co-incident with the final upward deflection on the N_2 record and this was a consistent finding in the majority of the records. It can be interpreted as manifesting an increase in airway resistance due to parital airway closure in the dependent regions of the lungs. The pressure record probably provides more direct evidence of the closure phenomenon than the N_2 record. In this subject the CV_{FO} was 8% of her vital capacity and 7% by CV_{N2}. A similar record is reproduced in Fig 3, this time from a 67 year old smoker, one of the "normal" volunteers. The CV_{N2} clearly occurred at a considerably higher lung volume, namely 1.22 liters, before the end

of his vital capacity (25%). Again the pressure record distinctly signals the event of closure by the increase in amplitude. In this record as in most others a slight but gradual increase in pressure amplitude occurs throughout expiration which is due to the declining elastic recoil of the lungs so that the airways are less distended than at full inspiration. Eccentric deviations from the sine-wave pattern as seen early on this record are artifacts due to fluctuations in the position of the glottis or vocal chords and are easily recognized as such. The third record (Fig 4) is from a 71 year old male, a smoker of 133 pack/years, who according to the routine tests was suffering from advanced chronic obstructive disease, not responsive to bronchodilators. The characteristic feature of this record is the steep angle of phase III in the N_2 record and the absence of any clear-cut phase IV. The lack of an alveolar plateau (phase III) seen in the normal N_2 records is due to unequal distribution of ventilation and sequential emptying of alveoli which completely obscures the CV phenomenon. Not so on the pressure record. Here a distinct increase in amplitude is clearly recognizeable and the corresponding CV_{FO} turned out to be 52% of vital capacity on the right record and 58% on the left. Thus his CV was well above his functional residual volume (FRC Fig 4) so that s substantial number of airways must have been closed at the end of normal expiration. This probably accounted for his severe hypoxemia with an arterial P_{O2} of 43 Torr. This and several other cases, where the pressure record gave a clear indication of CV, while the N_2 record did not, lead to the conclusion that the FO method is superior to the N_2 method for CV, particularly in patients with severe obstructive impairment and poor mixing efficiency.

A statistical analysis of the 30 cases for which both CV_{N2} and CV_{FO} were available showed the following comparison:

	$\%CV_{N2}$	$\%CV_{FO}$
$\bar{x}$	16.7%VC	14.7%VC
SD	8.4%	7.2%

According to the mean values CV_{FO} was slightly less than CV_{N2}, but this difference was not statistically significant by paired comparison.

There was a highly significant correlation between CV_{N2} and CV_{FO} ($r = .62$; $p < .0001$). The regression for $\%CV_{N2}$ (y) versus $\%CV_{FO}$ (x) was:

$$y = 0.537x + 8.80$$

The reproducibility of both methods was tested by having the same individual repeat the maneuver three times within a few minutes. The mean coefficient of

variation for CV%VC was close to 15% in either method which is acceptable. But the accuracy of measurement is improved by averaging several determinations which are neither time consuming nor difficult to perform.

REFERENCES

1. Dollfuss, R.E., J. Milic-Emili and D.V. Bates. Regional ventilation of the lungs studied with boluses of 133-Xenon. Respir. Physiol. 2:234-246, 1967.

2. Leblanc, P., F. Ruff and J. Milic-Emili. Effects of age and body position on "airway closure" in man. J. Appl. Physiol. 28:448-451, 1970.

3. Macklem, P.T. Obstruction in small airways-a challenge to medicine. Am. J. Med. 52:721-724, 1972.

4. NASA Contract NAS9-14472. Specialized physiological studies in support of manned space flight. Report February, 1975, Part II. A comparison of the closing volume test with other pulmonary function measurements.

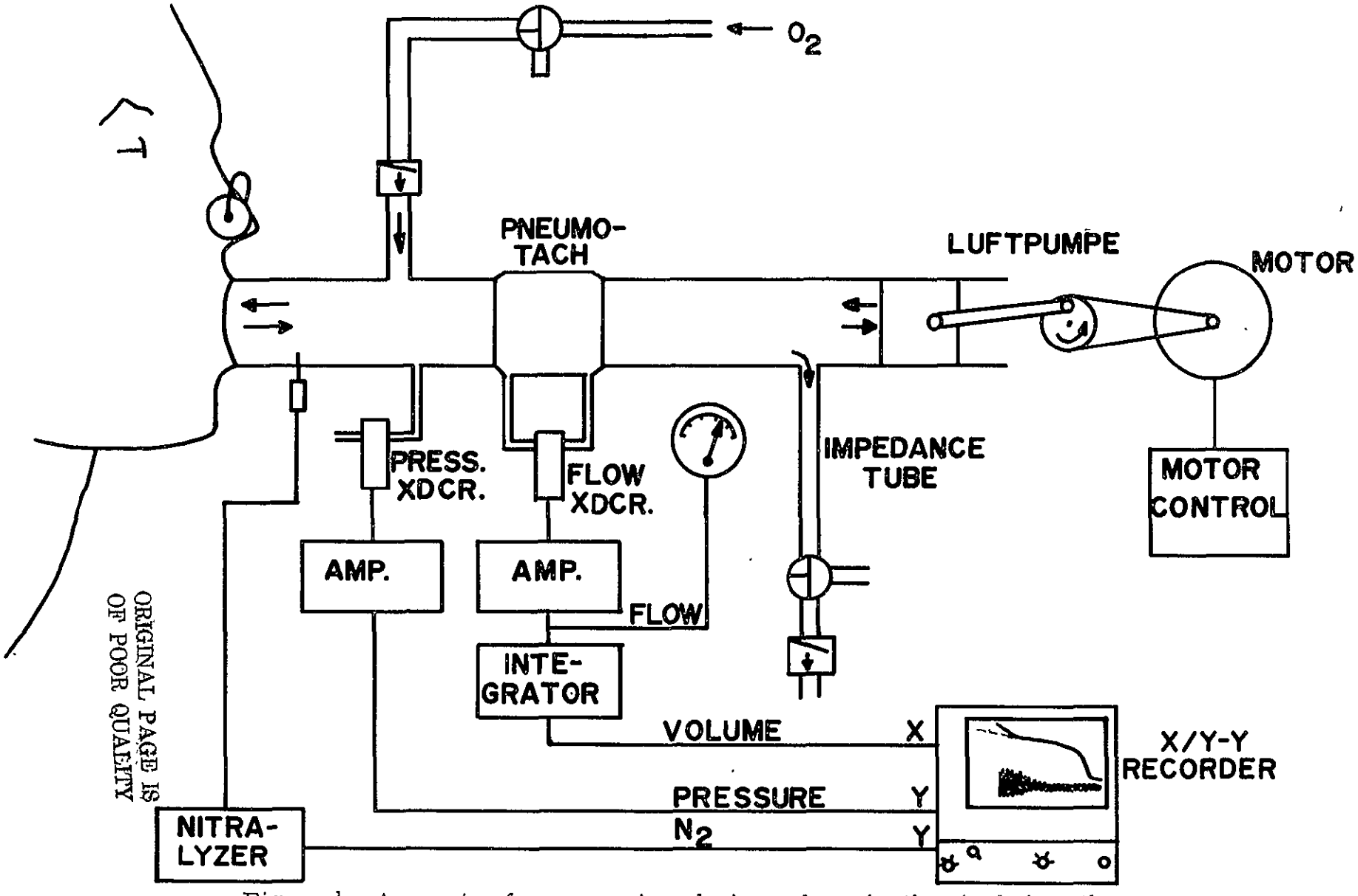


Figure 1. Apparatus for measuring closing volume by the single breath N_2 method and by forced oscillations simultaneously.

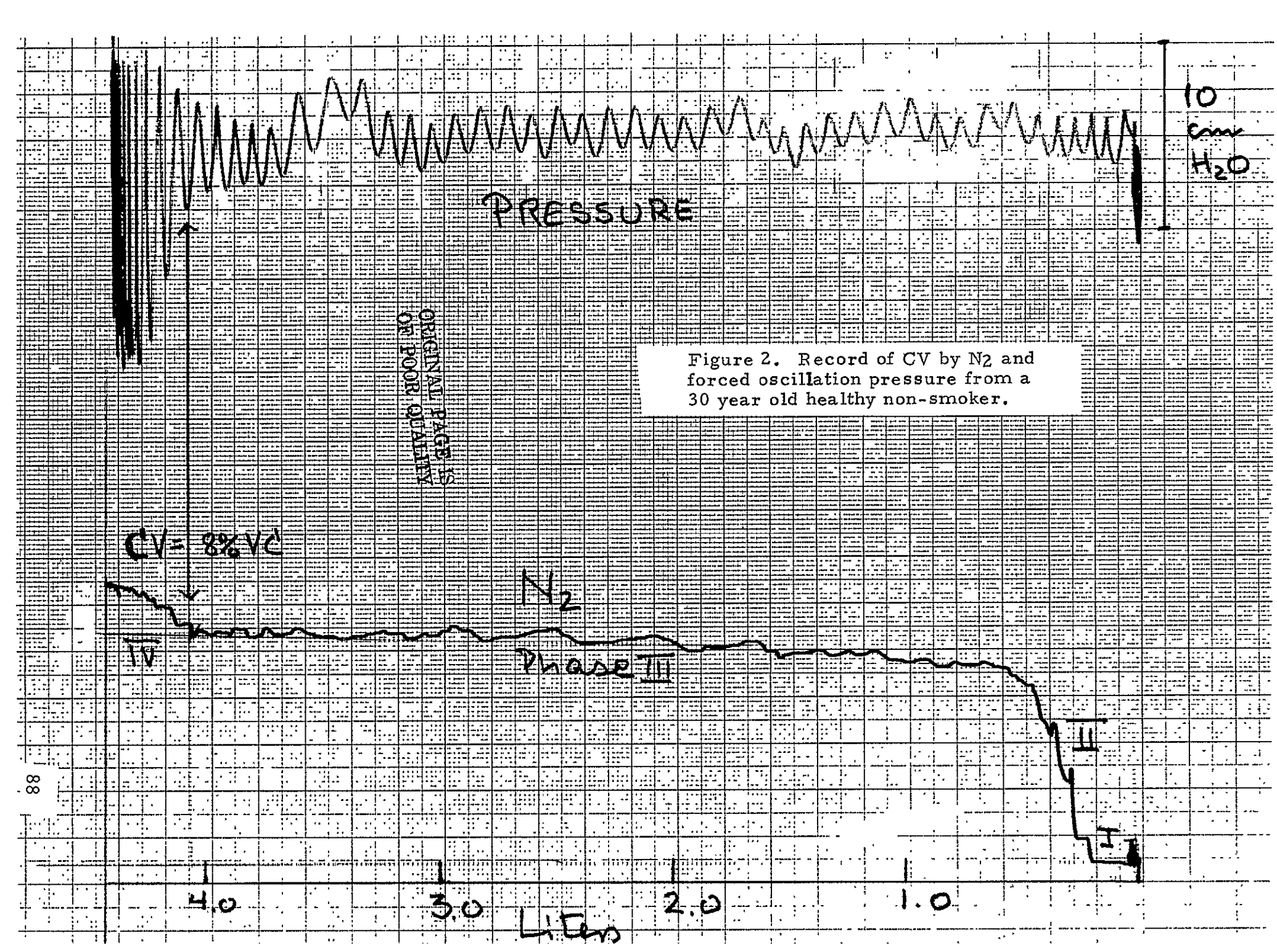


Figure 2. Record of CV by N_2 and forced oscillation pressure from a 30 year old healthy non-smoker.

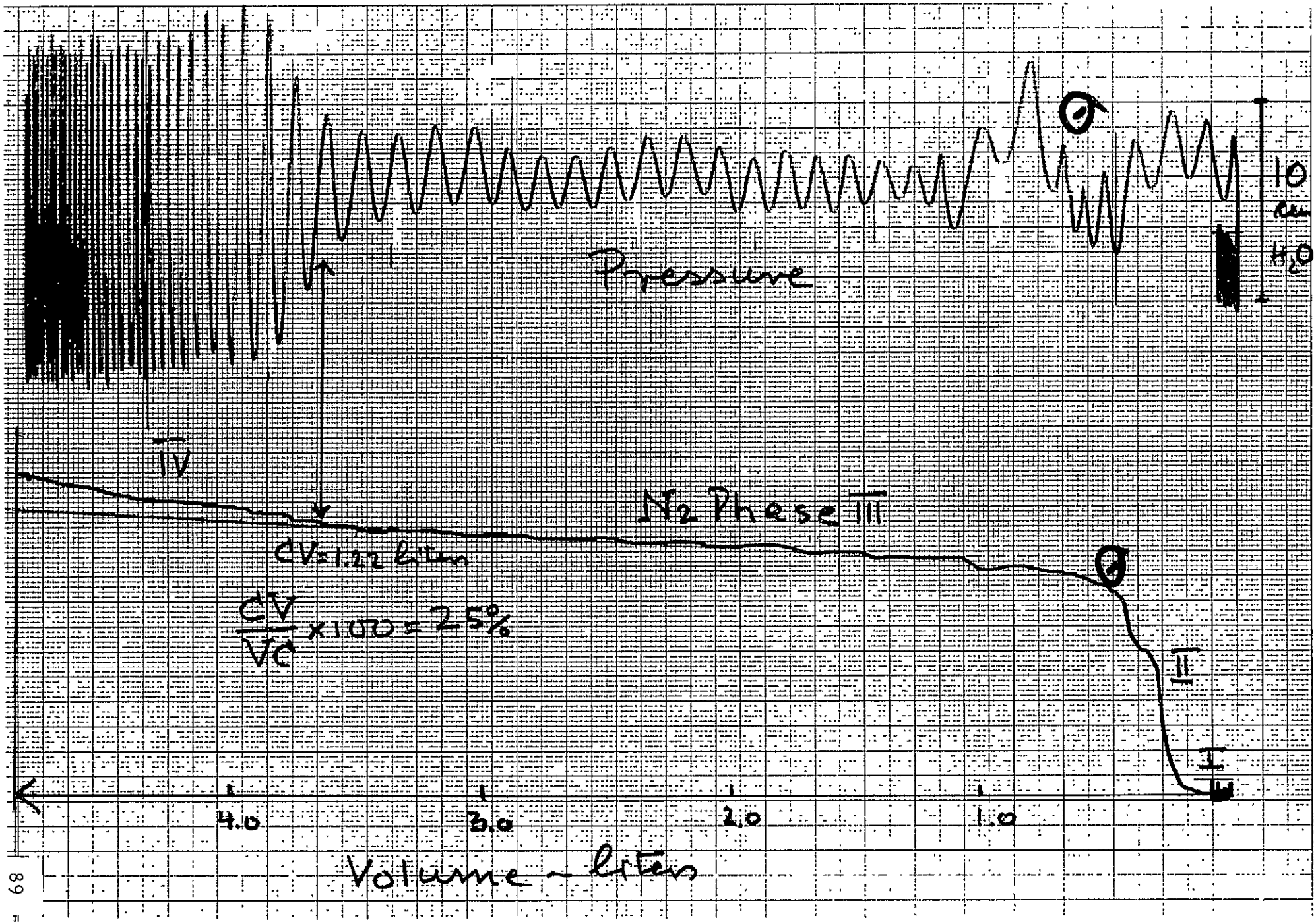


Figure 3. Record of CV by N_2 and forced oscillation pressure from a 67 year old healthy smoker.

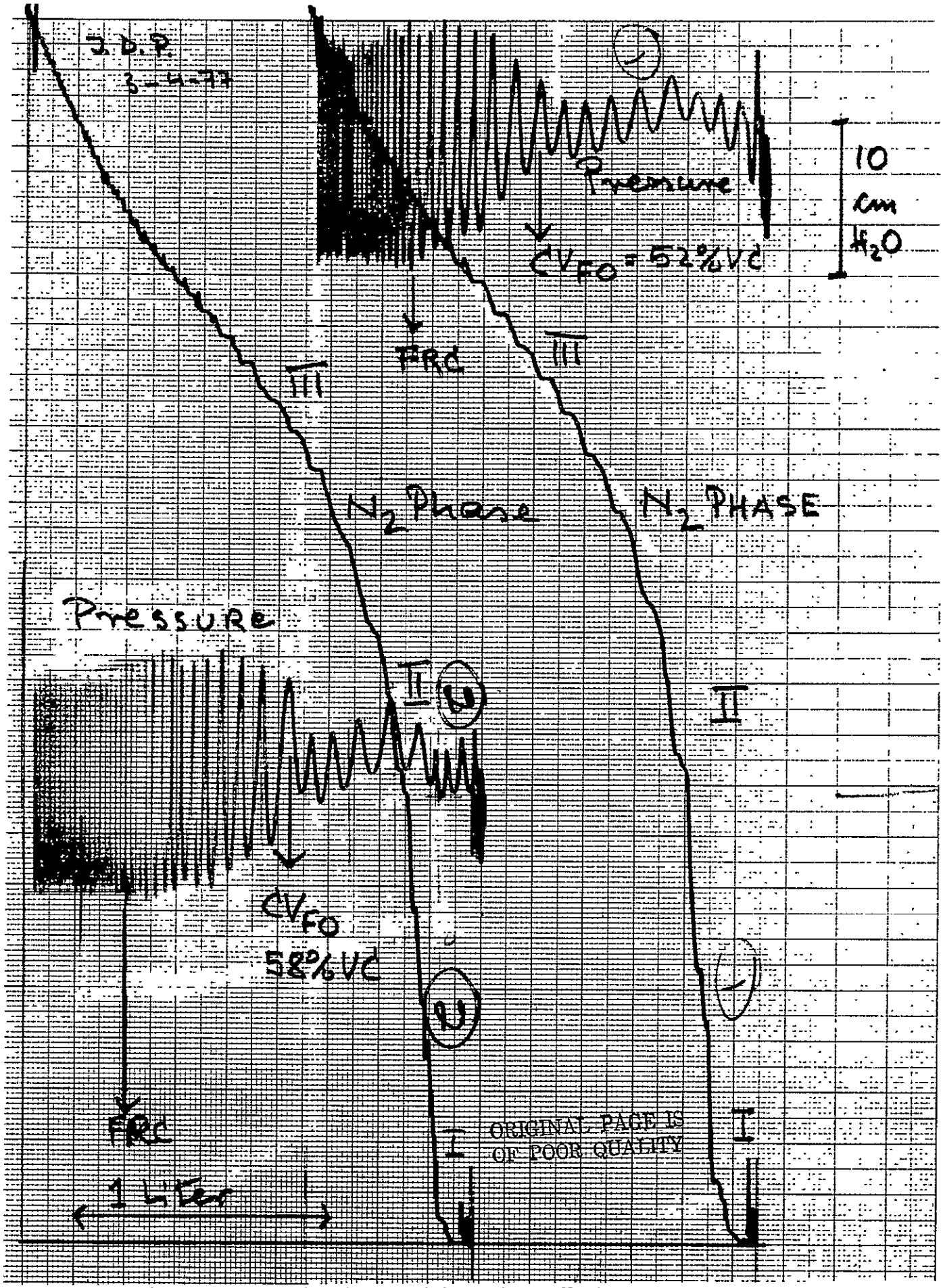


Figure 4. Two records of N_2 and forced oscillation pressure from a 71 year old heavy smoker with severe obstructive disease. Note that no CV can be detected on the N_2 record but is clearly defined on the pressure record.

TABLE 1

NORMALS

Subject	VC (l)	RV (l)	FRC (l)	$(CV\%VC)_{FO}$	$(CV\%VC)N_2$
1	4.20	1.53	3.13	8	6.6
2	6.18	1.84	4.47	7	6.4
3	4.08	1.98	4.42	12	22.2
4	3.22	1.04	2.78	20	27.7
5	5.81	0.51	2.32	7	7.7
6	4.82	2.52	3.99	22	28.6
7	3.13	1.55	2.86	18	22.0
8	6.20	1.32	3.75	12	12.3
9	3.92	1.44	2.55	15	19.2
10	3.73	1.04	3.14	12	12.5
11	4.61	0.88	3.00	15	8.0
12	4.73	0.90	2.28	6	12.1
13	4.40	0.94	2.29	9	10.5
14	3.01	1.22	2.57	16	25.9
15	5.71	1.01	3.21	6	4.9
16	3.89	0.58	2.02	11	12.0
17	5.76	1.60	3.73	7	13.5
18	4.57	0.94	30.6	8	11.4
			PATIENTS		
1	2.52	1.93	2.09	10	15.5
2	4.27	1.88	3.32	7	21.6
3	2.12	3.94	4.76	42	23.1
4	3.50	1.54	3.56	12	8.2
5	3.04	1.71	2.84	24	23.7
6	2.72	1.68	2.55	16	27.2
7	4.12	1.60	4.69	27	27.0
8	2.13	0.74	1.44	34	20.0
9	3.87	1.81	2.42	12	18.5
10	3.31	2.57	3.59	18	22.8
11	2.33	0.50	1.10	16	14.0
12	4.56	2.57	4.20	12	15.5

PART V

ACOUSTIC KINETOCARDIOGRAPHY--
A NEW TECHNIQUE FOR RECORDING CARDIAC MOTION

ABSTRACT

Preliminary evaluation of a non-invasive, non-contact approach to measurement of chest wall motion during and after lower body negative pressure has been accomplished. The procedure, called acoustic kinetocardiometry, involves use of a device developed in the Biomedical Engineering Department at the Lovelace-Bataan Medical Center. A dual transducer probe is placed a few centimeters from the chest,and transmitted and reflected low frequency ultrasonic waves are compared by a phasemeter. Movements of the chest of less than 0.1 mm may be faithfully recorded. Because movement of the precordium is caused by impingement of the heart against the chest wall, it reflects changes in size and compliance of the ventricles. A superficial analysis of data from eight subjects suggests that the acoustic kinetocardiogram may reflect changes in stroke volume and ventricular filling occuring during and after imposition of orthostatic stress by lower body negative pressure.

INTRODUCTION

During the final three months of the contract period we have initiated a study of the value of acoustic kinetocardiography as a means of non-invasive assessment of cardiac function during lower body negative pressure (LBNP). Kinetocardiometry is the measurement of absolute precordial motion, usually in the frequency range of direct current to 50 Hz. It is a technique that has been known for some time (3) but has not been applied widely because of instrumentation problems that make testing tedious and data output circumspect.

Most of the problems with previously developed kinetocardiometers are directly related to the requirement for a transducer in contact with the chest wall. With a contact transducer, positioning of the instrument is tedious and there is an inherent distortion of data output due to varying degrees of source loading. A Lovelace bioengineer has developed a device (2) during the past year which measures chest wall motion without physically contacting the chest--a major advance. The instrument in shown in use in Fig 1. Its output is referred to as the acoustic kinetocardiogram (AKCG). The technique is based on low frequency ultrasound and has therefore been called acoustic kinetocardiography. The theory of operation of the device is quite simple. Basically, an ultrasonic beam is transmitted toward the precordium from a fixed crystal about 10 inches above the chest wall. The beam bounces off the chest wall and returns to a second crystal (the receiving crystal) alongside the transmit crystal. In order to detect chest wall motion then, it is only necessary to monitor the changes in transit time from transmitter-to-chest-to-receiver.

For clinical purposes, kinetocardiograms are recorded from several positions on the chest. These positions are denoted as the "K" positions with subscripts identifying the location from which a tracing is recorded. The first number in the subscript identifies the vertical line corresponding to the electrocardiographic precordial lead or "V" position and the second number identifies the intercostal space. For instance a kinetocardiogram recorded from the K_{24} position is made with the probe placed over position V_2 (or just to the left of the sternum) in the fourth intercostal space. A schematic drawing by Eddleman (3) of the normal kinetocardiogram at several positions is shown in Fig 2 along with a caption identifying the landmarks in the waveforms.

Physiological alterations that are most likely to be reflected in the kinetocardiogram or other recordings of precordial motion are those involving change in compliance and size of the ventricles. Pathological changes that result in

altered compliance include myocardial infarction and aneurysm. Examples of those that result in hypertrophy are systemic or pulmonary arterial hypertension. Any of these may result in systolic bulging which is represented by large, sustained outward movements on the kinetocardiogram that become more pronounced with increasing severity of the disease. Right and left ventricular hypertrophy may be distinguished by the fact that outward movements are more prominent in the K_{45}, K_{46} and K_{55} positions in left ventricular hypertrophy and more prominent in the K_{14} and K_{24} positions in right ventricular hypertrophy. Records taken from two patients at the K_{44} position using the Lovelace acoustic kinetocardiometer are shown in Figs 3and 4. In Fig 3 a large outward movement (above the baseline) is consistent with elevated pulmonary artery pressure which was confirmed during cardiac catheterization. The recording in Fig 4 is from a patient with a ventricular aneurysm. Note the large, sustained outward movement during systole.

It may also be expected that changes in the volume and position of the ventricles during lower body negative pressure should be reflected in the kinetocardiogram. These changes can also be measured in terms of alterations in stroke volume or cardiac vector, but they require measurement of cardiac output in the first case, and extensive electrocardiography in the second case. Kinetocardiography is a potential tool, then, for simple, non-invasive, non-contact evaluation of cardiac function during changes in orthostatic stress both in the laboratory and during flight in space.

METHODS

During the lower body negative pressure studies, kinetocardiograms were recorded from the K_{45} position near the cardiac apex. Tracings were made with the subject lying in the LBNP box at ambient pressure, during the fourth minute at each level of negative pressure and during the first and fourth minutes following restoration of ambient pressure.

For purposes of timing the events in the kinetocardiogram, the electrocardiogram (ECG), phonocardiogram (PCG), and arterial pulse wave were recorded simultaneously with the KCG. Usually the arterial pulse is recorded from a microphone placed over the carotid artery. However, for the LBNP studies the pulse wave was recorded from the pinna of the ear using a Hewlett-Packard photoplethysmographic ear densitometer (ED). This device provided reliable waveforms for timing purposes while avoiding the need for a neck strap. In addition it is felt

that the amplitude of the ED waveform may reflect changes in stroke volume.

Data was continually recorded on magnetic tape by a Hewlett-Packard Model 3907C tape recorder and annotated so that appropriate intervals could be replayed through a Honeywell Model 906B Visicorder at a later time.

RESULTS AND DISCUSSION

Data has been collected on a total of 30 subjects and preliminary analysis has been completed on eight. The approach used by Eddleman has been generally followed for analysis of the acoustic kinetocardiographic data. According to his procedure a baseline is drawn 0.04 sec after the onset of the QRS complex since it is expected that movements related to ejection begin near or shortly after this point. Polarity is arranged so that an outward movement of the chest wall is represented by an upward deflection in the kinetocardiogram. Eddleman proposes that the records be digitized for computer processing and that amplitudes by expressed as a percentage of total amplitude and the cardiac cycle length normalized to 0.836 sec. We have found it simpler, however, to normalize the cardiac cycle length to 1.00 sec.

In the preliminary analysis conducted to date the maximum systolic amplitude (Ampl.) and the amplitude of the total systolic retraction (TSR) have been measured from 3 - 5 consecutive intervals in each recording. The TSR is the major systolic inward (below the baseline) movement of the AKCG and occurs during ejection. The total amplitude includes the TSR but also includes any of the normally small outward movements of early systole such as the right ventricular movement (RVM) and the left ventricular thrust (LVT).

Data from the preliminary analysis is characterized by a good deal of inter-subject variability. However, the trend in most of the subjects is for the major inward systolic movement to become progressively smaller during increasing LBNP exposure. This may be appreciated by comparing the pre-test and -60 Torr recordings in Fig 5. The Ampl. and TSR return to values equal to or greater than the pre-test measurements in the first tracings made after restoration of ambient pressure. These changes parallel previously identified changes in stroke volume (5) during LBNP.

An indirect indication that the decrease in the amplitude of the AKCG reflects decreases in stroke volume is seen in Fig 7 where the regression of the heart rate (x) with total AKCG amplitude (y) for the eight subjects at -60 Torr is plotted. The equation of the line is $y = 0.0037\ x - 0.489$ and the correlation coefficient

C-8

($r = 0.67$) is marginally significant ($p < .10$). These data show that the subjects with the highest heart rates (and the lowest stroke volumes if cardiac output did not change) had the smallest AKCG amplitudes at -60 Torr.

Two studies (1, 4) using traditional high frequency ultrasound have shown that end-diastolic volume is reduced during LBNP indicating that the decrease in stroke volume is due to decreased ventricular filling. An interesting feature of the AKCG's from these eight subjects is the change in the morphology of the filling and atrial movements occurring immediately after return to ambient pressure following LBNP. Although characteristics of the movements have not been quantitated they appear qualitatively to become more prominent following LBNP perhaps reflecting the increase in venous return and increase in cardiac filling.

This preliminary analysis of the AKCG data is very limited and has resulted in extraction of only a small fraction of the data contained in the recordings from the 30 LBNP studies completed to date. However, even these very preliminary results suggest that acoustic kinetocardiography may be a useful tool for evaluating cardiac function during changes in orthostatic stress.

REFERENCES

1. Ahmad, Masood, C. Gunnar Blomquist, Charles B. Mullins, and James T. Willerson. Left ventricular function during lower body negative pressure. Aviat. Space and Environ. Med. 48:512-515, 1977.

2. Davis, Jerry G. An acoustic transducer for application in kinetocardiography. IEEE Transactions on Biomedical Engineering. 24:484-486, 1977.

3. Eddleman, E.E., Jr. Kinetocardiography. In: Non-Invasive Cardiology. Arnold M. Weissler, Ed. New York: Grune & Stratton. 1974, pp. 227-273.

4. Nutter, Donald O., Victor W. Hurst III, and Raymond H. Murray. Ventricular performance during graded hypovolemia induced by lower body negative pressure. J. Appl. Physiol. 26:23-30, 1969.

5. Stevens, Paul M. and Laurence E. Lamb. Effects of lower body negative pressure on the cardiovascular system. The Am. J. Cardiol. 16:506-515, 1965.

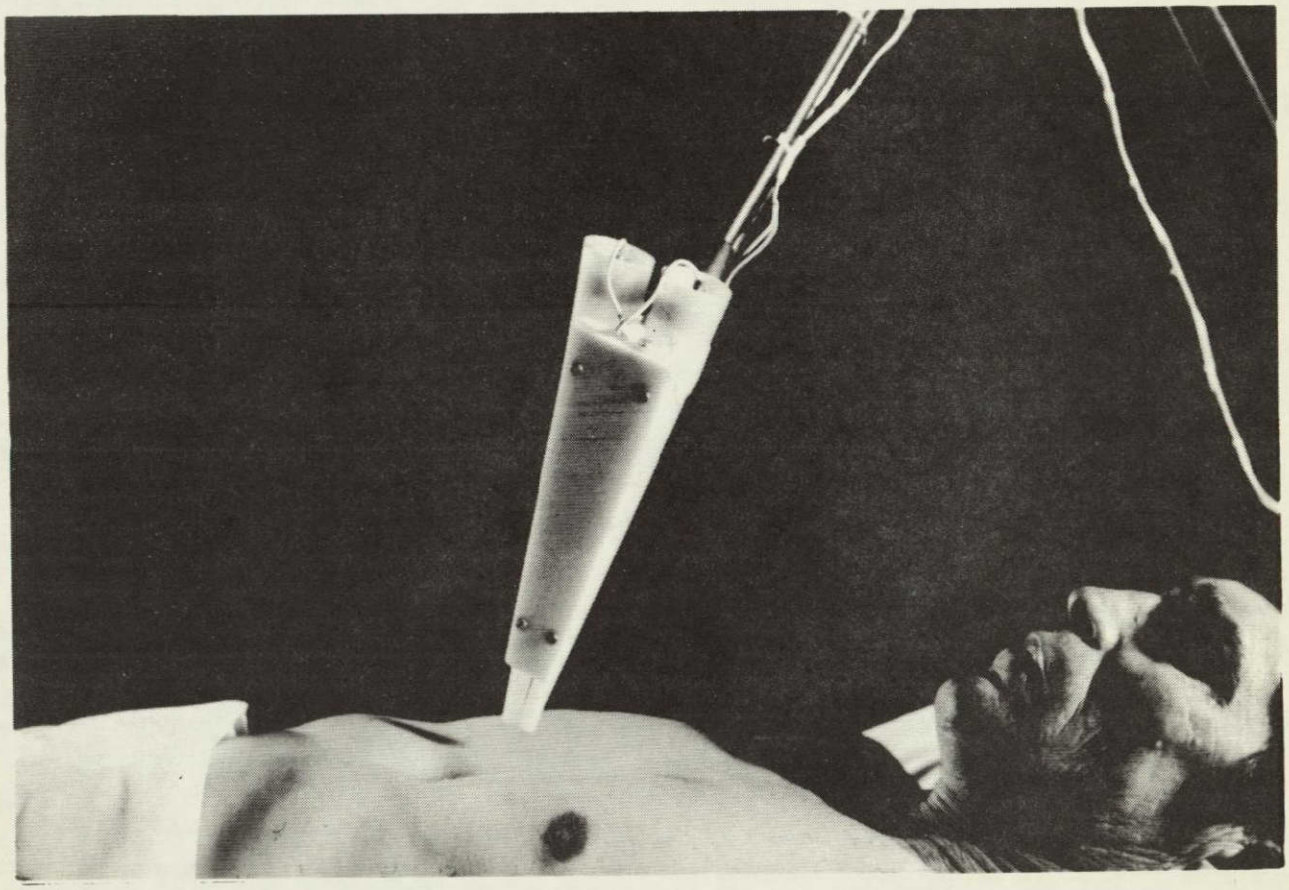


Figure 1. The acoustic kinetocardiometer in operation.

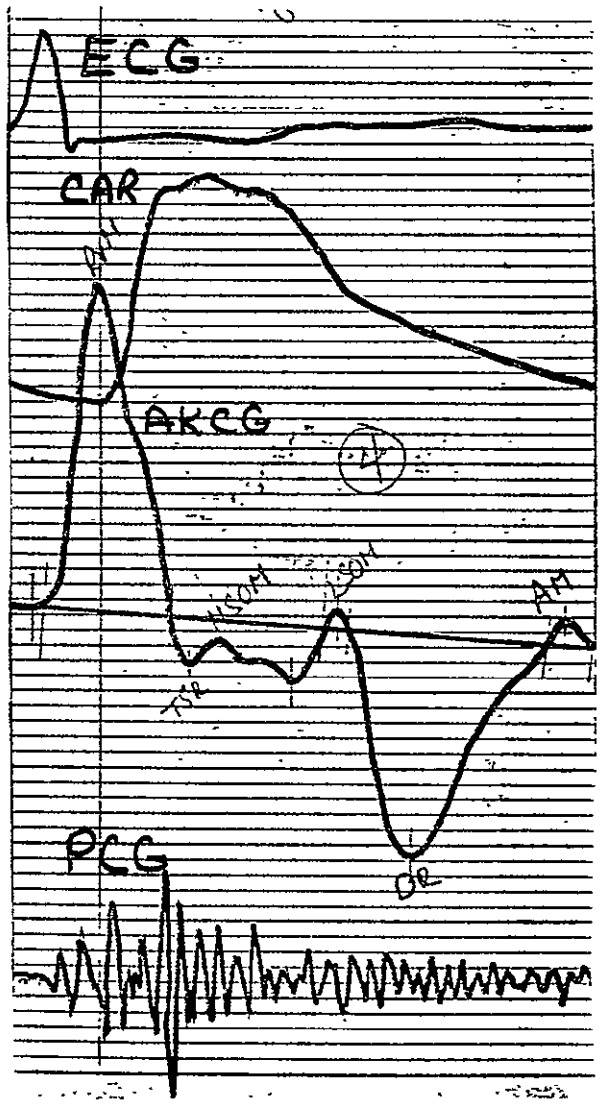


Figure 3. Tracing from a patient with elevated pulmonary artery pressure, position K44.

ECG: Electrocardiogram
CAP: Carotid artery pulse
AKCG: Acoustic kinetocardiogram
PCG: Phonocardiogram

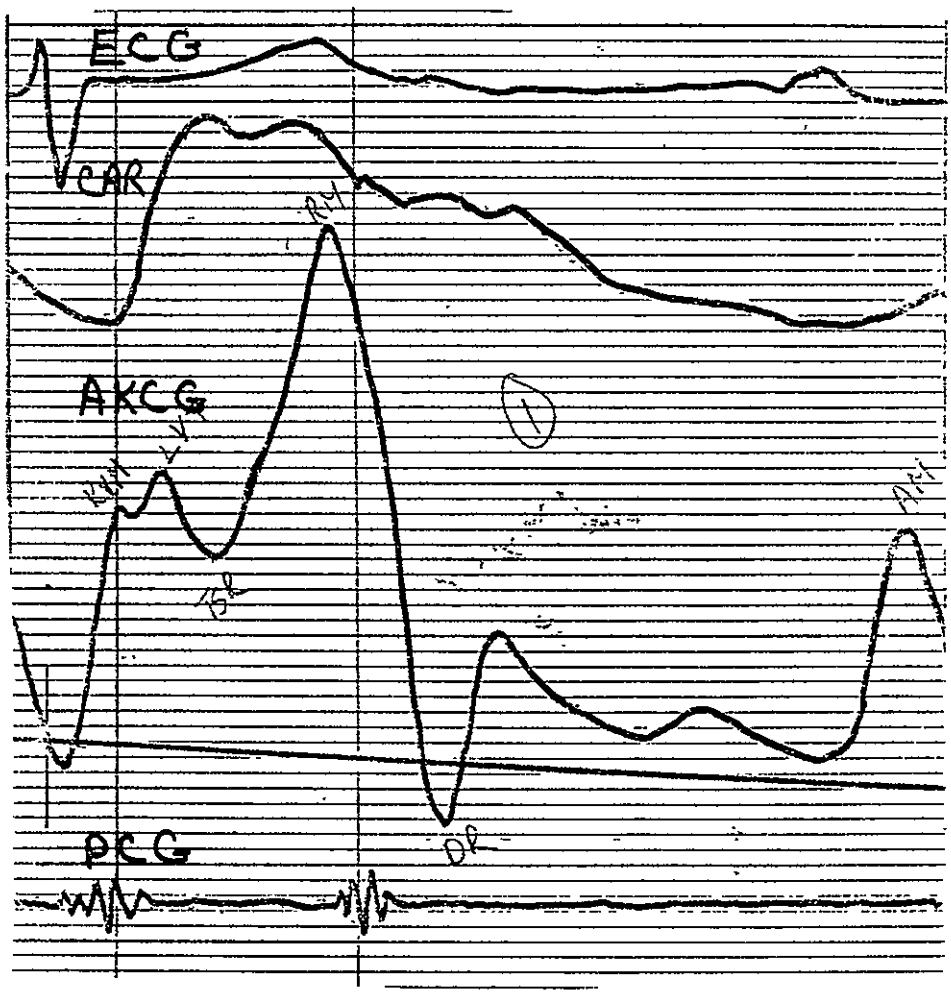
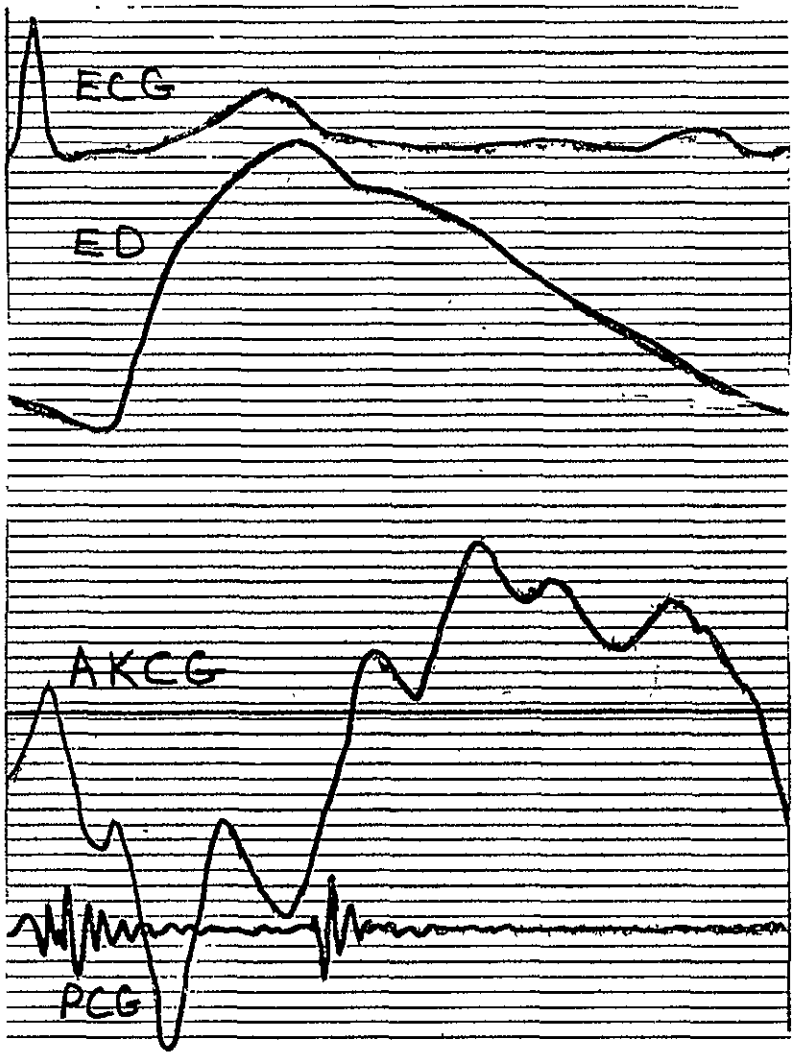
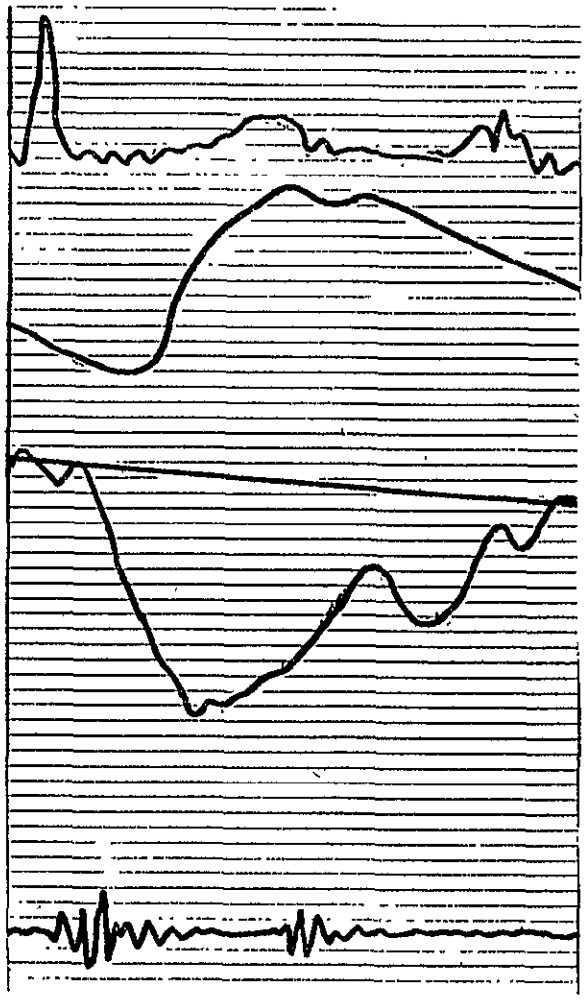


Figure 4. Tracing from a patient with ventricular aneurysm, position K_{44}.



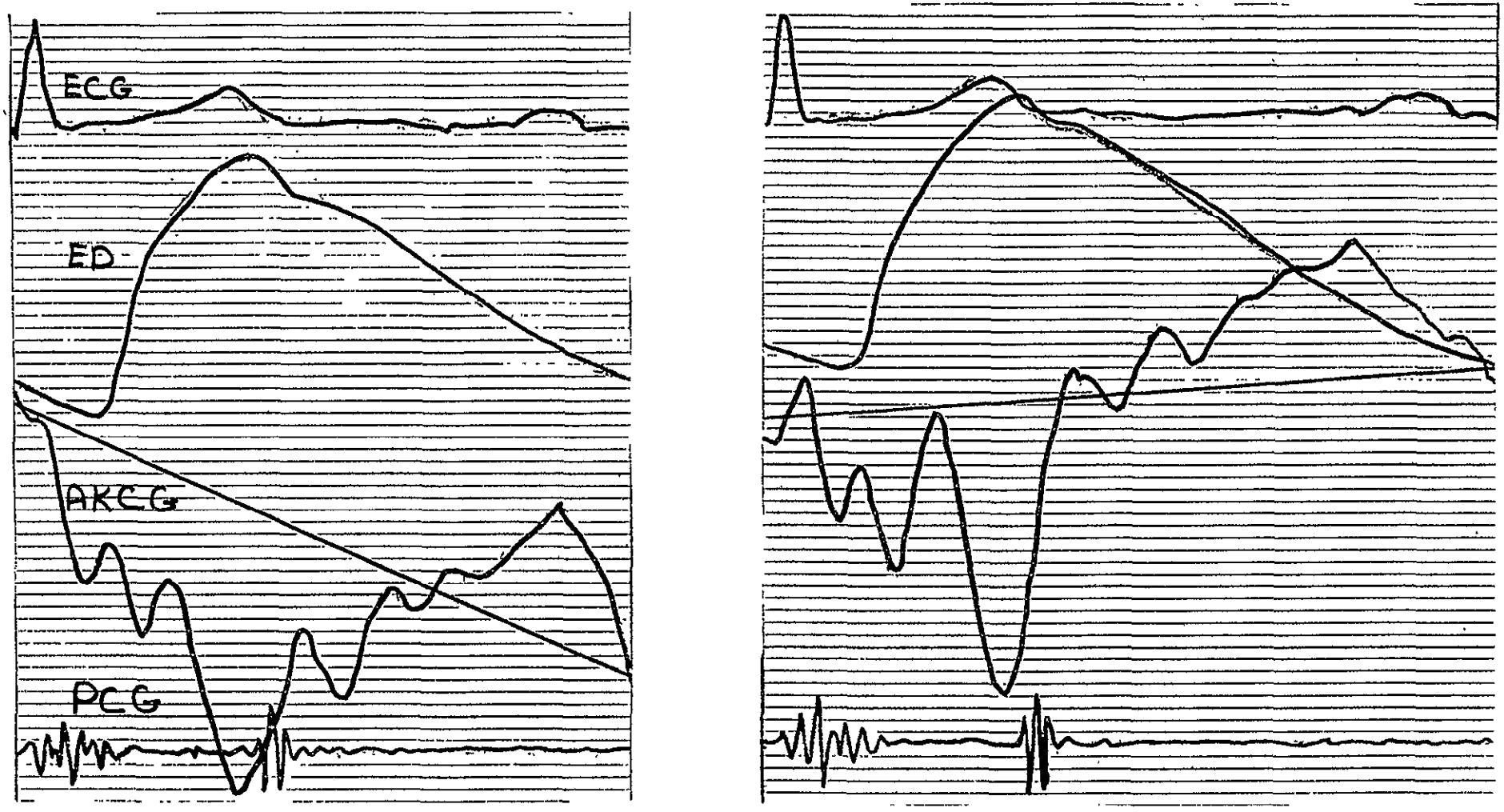
A. Pre-test, - Torr



B. LBNP, -60 Torr

Figure 5. Acoustic kinetocardiograms at position K_{45} before and during LBNP.

ECG: Electrocardiogram
ED: Ear densitometer
AKCG: Acoustic kinetocardiogram
PCG: Phonocardiogram



A. 1st min after return to 0 Torr.

B. 4th min after return to 0 Torr

Figure 6. Acoustic kinetocardiograms following LBNP

Figure 7. Regression of acoustic kinetocardiogram amplitudes with heart rate.